Medical Library
Hospital Library

VOLUME LXXVII NUMBER 3

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

September, 1945

A Study of A Food-Borne Epidemic of Tonsillitis and Pharyngitis Due to β-Hemolytic Streptococcus, Type 5. COMMISSION ON ACUTE RESPIRATORY DISEASES 143

Suppression as an Adjunct to the Therapy of Malaria in Non-Malarial Areas. ROGER A. LEWIS, Captain AND FRANK W. KIBBE, 1st Lieutenant, *Medical Corps, Army of the United States* 211

A Study of Spasticity and Paralysis. PHILIP F. WAGLEY 218

Two Cases of Periarteritis Nodosa Occurring in the First Month of Life. HARRY A. WILMER, PH.D., M.D. 275

Book Reviews 287

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

COPYRIGHT, 1945, BY THE JOHNS HOPKINS PRESS

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, HENRY N. HARKINS

ASSOCIATE MANAGING EDITOR, JOHN A. LUETSCHER, JR.

EDITORIAL BOARD

E. Cowles Andrus — James Bordley, III
Charles R. Austrian — Chalmers L. Gemmill
W. Halsey Barker — John Eager Howard
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore-5, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefor adjusted accordingly.

Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2

THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

A STUDY OF A FOOD-BORNE EPIDEMIC OF TONSILLITIS AND PHARYNGITIS DUE TO β-HEMOLYTIC STREPTOCOCCUS, TYPE 5[1]

COMMISSION ON ACUTE RESPIRATORY DISEASES

Fort Bragg, North Carolina

I. INTRODUCTION

Advances in knowledge of β-hemolytic streptococcal infections have been made in recent years by the application of newer techniques in bacteriology and immunology and by further applications of clinical and epidemiological methods. Most of the recent studies of streptococcal respiratory disease have been made on sporadic or epidemic contact or air-borne infections, and the opportunities to study food-borne epidemics have been few. Such an opportunity arose at Fort Bragg in November 1943.

The epidemic was confined to members of two companies of an air-borne infantry regiment. The causative agent was a strain of β-hemolytic streptococcus of Group A, type 5, and the source of the primary cases was believed to be food served at breakfast on November 17. One hundred patients with type 5 streptococcal infection of the throat were hospitalized from a group consisting of 32 officers and 228 enlisted men.

[1] This investigation was supported through the Commission on Acute Respiratory Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army, and by grants from the Commonwealth Fund, the W. K. Kellogg Foundation, the John and Mary R. Markle Foundation, and the International Health Division of the Rockefeller Foundation to the Board for the Investigation and Control of Influenza and Other Epidemic Diseases for the Commission on Acute Respiratory Diseases.

Members and professional associates of the Commission on Acute Respiratory Diseases are: John H. Dingle, Major, M.C., A.U.S., Director; Theodore J. Abernethy, Major, M.C., A.U.S.; George F. Badger, Major, M.C., A.U.S.; Joseph W. Beard, M.D.; Norman L. Cressy, Major, M.C., A.U.S.; A. E. Feller, M.D.; Irving Gordon, M.D.; Alexander D. Langmuir, Major, M.C., A.U.S.; Charles H. Rammelkamp, Jr., M.D.; Elias Strauss, Captain, M.C., A.U.S.; and Hugh Tatlock, Captain, M.C., A.U.S.

Extensive clinical, laboratory, and epidemiological studies were carried out. The patients were segregated on special wards where they were examined daily for the entire 10-day period of hospitalization. Daily throat cultures were taken and appropriate clinical laboratory studies made. On the initiative of Lt. Col. W. B. Daniels, Chief of the Medical Service, alternate patients were treated with sulfadiazine in order to evaluate the effect of chemotherapy on the course of the disease. Follow-up studies were made 3 and 6 weeks after the epidemic to detect late complications.

Field studies were undertaken in the two affected companies of the regiment (G and Hq) and in a "control" company (H) which was housed in adjacent barracks but served by a different mess hall. Throat cultures were taken on all members of G and Hq Companies on November 20, 22, 25 and 29, and on December 9 and 30. Less frequent culture surveys were made in H Company during the same period of time. Blood specimens were collected from all members of the three companies at periodic intervals for 6 weeks after the recognition of the epidemic. A quarantine was imposed on G and Hq Companies for 3 weeks beginning on November 20.

The purpose of this report is to bring together the results of these various types of investigation in an attempt to describe, in as complete a manner as the data permit, 1) the natural history of a food-borne epidemic of streptococcal pharyngitis and tonsillitis, and 2) the modifications of the expected features of the disease resulting from therapeutic and control measures.

II. EPIDEMIOLOGICAL STUDIES

The chronological sequence of development of the epidemic is illustrated in figs. 1 and 2; the former indicates the date of onset of symptoms of hospitalized and non-hospitalized cases[2]; the latter the date of discovery of healthy carriers.

Primary and secondary attack rates. The definitions of the terms "primary" and "secondary" were, of necessity, arbitrary but were made after consideration of all the facts elicited in regard to the time

[2] Non-hospitalized cases represented subjects who made dispensary visits for symptoms referable to the respiratory tract within a week after type 5 streptococci were first isolated in their throat cultures.

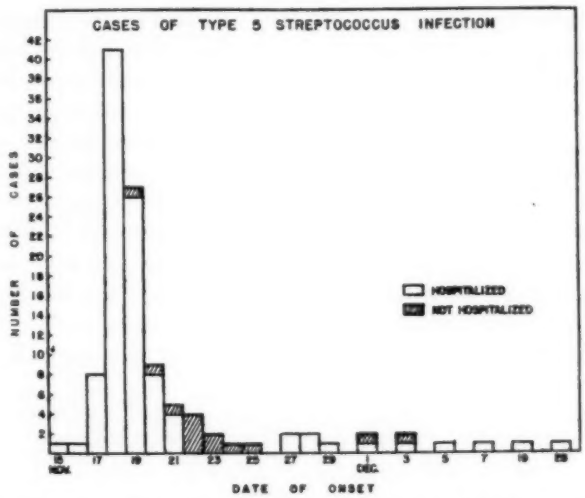


FIG. 1. DISTRIBUTION OF CASES OF TYPE 5 STREPTOCOCCUS INFECTION BY DATE OF ONSET OF SYMPTOMS

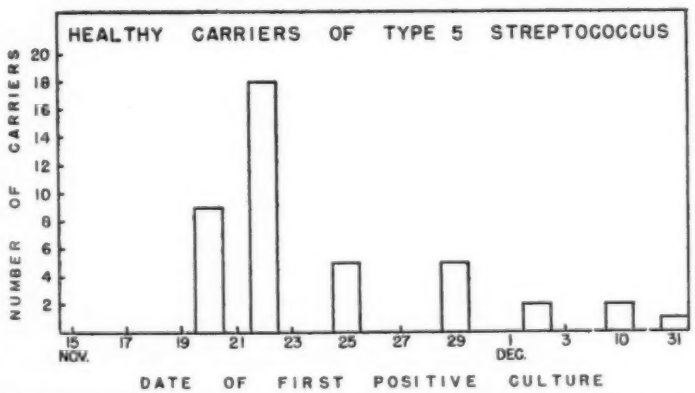


FIG. 2. DISTRIBUTION OF HEALTHY CARRIERS OF TYPE 5 STREPTOCOCCI BY DATE OF FIRST POSITIVE CULTURE

of original infection and incubation period. Primary cases were defined as subjects who became ill and harbored type 5 streptococci at the time of the first culture survey on November 20. Fig. 1 indicates

that more than 75 per cent of the total number of cases had an onset of symptoms on or before that time. Epidemiological evidence dated the time of primary infection as the morning of November 17. Two cases had a clinical onset before November 17; this discrepancy may have been due to an error in history-taking or to the presence of respiratory symptoms due to other causes antedating the infection with type 5 streptococci. Secondary cases were defined as those who did not harbor type 5 streptococci on November 20 or before but who subsequently became ill and acquired the organisms. "Early" secondary cases were those who acquired the organisms before November 27, and "late" secondary cases those who first harbored the organisms after that date. Healthy carriers were classified by the same cultural criteria as cases.

Since 27 men had already become ill by noon of November 18, there were numerous foci of infection scattered throughout the group for 48 hours before the first culture survey was made. It is therefore entirely possible that some of the cases and carriers classified as "primary" may, in fact, have been infected secondarily by contact in the barracks with earlier cases or carriers. However, the separation made of primary and secondary cases and carriers seemed the most reasonable with the data available.

Primary and secondary attack rates were determined on the group of 228 enlisted men in G and Hq Companies who were present on November 17 and remained under observation until December 31. During this period all hospital admissions were studied, dispensary visits counted, and 6 periodic culture surveys made. The primary attack rate for this group was 41.7 per cent (table 1). Of these 86 were primary cases and 9 carriers. The secondary attack rate, among those exposed to risk, was 30.1 per cent, of which somewhat less than one-half were secondary cases and slightly more than one-half were secondary carriers. In the course of 6 weeks from the beginning of the outbreak, 59.2 per cent of the men in the group acquired type 5 streptococci; 45.6 per cent were cases and 13.6 per cent carriers.

The case to carrier ratio of the primary infections was approximately 10 to 1 which suggested a massive dose of infection and indicated that almost all subjects who acquired the infectious agent at the time of the

original seeding became clinically ill. Among the secondary infections, the case to carrier ratio was approximately 1 to 1. More than two-third of the healthy carriers appeared to acquire the organisms as a result of secondary contact spread.

Effect of quarantine. A rigid quarantine of G and Hq Companies was put into effect on November 20 and maintained for 3 weeks. The training program was continued but no intermingling was permitted of men from these two companies and the other units of the regiment. On December 8 a member of H Company, housed in barracks adjacent to G and Hq Companies, became ill and was hospitalized with type 5 streptococcal tonsillitis. This was the only instance of cross-infection

TABLE 1

Primary and Secondary Attack Rates in 228 Enlisted Men in G and Hq Companies

TYPE OF INFECTION	STRENGTH EXPOSED TO RISK	NUMBER			PER CENT		
		Cases	Carriers	Total	Cases	Carriers	Total
Primary	228	86	9	95	37.7	3.9	41.7
Secondary							
Early	133	11	13	24	8.3	9.8	18.0
Late	109	7	9	16	6.4	8.3	14.7
Total	228	104	31	135	45.6	13.6	59.2

encountered in the "control" company. No carriers of type 5 streptococci were detected in this organization during the period of quarantine or in the 3 weeks subsequent to it.

Source of infection. Because of the explosive nature of the epidemic and the concentration of cases with onsets on November 18 and 19, a common source of infection was immediately suggested. The further evidence of localization of the cases entirely to two companies served by a common mess and the absence of infection in an adjacent company served by a separate mess, pointed strongly to food as the vehicle of infection. From a consideration of the time of onset of illness and the probability of an incubation period of not more than 3 or 4 days, the search for the source of infection was concentrated on foods served at mess on November 16 or 17.

Investigation indicated that the milk supply could not have been infected unless it was contaminated after delivery to the mess hall. The milk was pasteurized and delivered in quart bottles from a large dairy which regularly served more than 10,000 troops on the Post.

On November 23 the enlisted personnel and officers were questioned regarding specific items of food eaten on November 16 and 17. Infection rates were calculated according to the history of eating specified foods, the infected individuals being those who harbored type 5 streptococci on the cultural survey conducted on November 20 (table 2). Infection rates among those who gave a definite history of eating or

TABLE 2

Relation of Presence or Absence of Type 5 Streptococci in Throat Cultures on November 20 to History of Eating Specified Foods on November 16 and 17

FOOD	TOTAL WITH FOOD HISTORY KNOWN		TYPE 5 STREPTOCOCCI PRESENT				P*
			Number		Per cent		
	Ate	Did not eat	Ate	Did not eat	Ate	Did not eat	
Spare ribs	129	9	73	4	57	44	0.47
Fruit salad	127	10	72	5	57	50	0.69
Creamed eggs	63	62	50	22	79	35	0.00001
Cauliflower	43	85	27	46	63	54	0.35
Noodles	95	31	59	15	62	48	0.16

* Probability that differences as great as these could arise from sampling.

not eating the particular items of food revealed a significant difference only for creamed eggs which were served at breakfast on November 17. Seventy-nine per cent of those who said they had eaten the eggs were infected whereas only 35 per cent of those not eating the eggs had positive cultures on November 20. The probability that this difference was the result of chance alone is 1 in 100,000. The source of infection of the 22 men who said they had not eaten creamed eggs could not be determined. The dietary interviews were conducted 6 days after the creamed eggs were served and were therefore subject to considerable error. It is also possible that some of these 22 cases may have been early secondary infections. At the time the investigation was made none of the food served before November 20 was available for bacteriological examination. The exact manner in which the creamed eggs

were prepared was not ascertained because of conflicting testimony. It was established, however, that the eggs had been boiled and then sliced by hand at least 10 hours before serving. None of the cooks harbored type 5 streptococci on November 20, nor was evidence obtained by examination or history of a recent infection in any of them.

Incubation period. Assuming that infection occurred at seven o'clock on the morning of November 17, the median incubation period of the primary cases was 38 hours. The onset of the median case was at nine o'clock on the morning of November 18. In 80 per cent of the cases the range of the incubation period was from 12 to 54 hours. One man injured his head on the evening of November 17 and was removed to the hospital. On the morning of November 20, while still in the hospital, he developed exudative tonsillitis from which type 5 streptococci were recovered. In this case which appeared to be a definite instance of primary infection, the incubation period was 72 hours. An incubation period of from 12 to 72 hours is in agreement with the findings in other food-borne streptococcal outbreaks in which a single exposure to a single source of infection was established (1).

Summary. In the course of an epidemic of pharyngitis and tonsillitis due to β-hemolytic streptococci of Group A, type 5, the primary attack rate among men exposed to risk was 41.7 per cent, of whom 91 per cent were cases and 9 per cent carriers (a case to carrier ratio of 10 to 1). The secondary attack rate was 30.1 per cent of whom approximately half were cases and half carriers (case to carrier ratio of 1 to 1). Altogether, in a 6 week period following the outbreak 59.2 per cent of all individuals in the group harbored type 5 streptococci at some time. In a group housed adjacent to the affected companies but segregated from them by a rigid quarantine, only one case of type 5 streptococcus infection occurred during a 6 week period. Epidemiological evidence indicated that the infection was food-borne and probably acquired from creamed eggs served at breakfast on November 17. The median incubation period for primary cases was 38 hours.

III. CLINICAL OBSERVATIONS

The clinical description of epidemic streptococcal tonsillitis and pharyngitis was based upon observations made on 91 cases hospitalized for respiratory disease from whom type 5 streptococci were isolated

on or before November 22. All but four were primary cases. Late secondary cases were excluded from these analyses. Non-hospitalized cases were also excluded from clinical analysis for lack of complete and comparable observations.

Methods of clinical study

All patients were seen immediately after admission to the hospital at which time a history was taken and a complete physical examination made. The occurrence of specified symptoms was recorded by 12-hour periods during the first 48 hours of illness and by 24-hour periods thereafter. Physical examination was made and history taken daily during the entire 10 day period of hospitalization. The severity of symptoms and signs was graded on a numerical scale, corresponding to mild, moderate, and severe (1, 2, and 3 respectively) for physical signs, and mild or moderate, and severe (2, and 3 respectively) for symptoms. The majority of patients were examined and questioned by only two observers throughout their hospital stay. Both observers frequently examined the same patient and compared their grading of the severity of symptoms and physical signs. As a result, it is believed that a high degree of comparability and uniformity was achieved in the collection and recording of clinical data.

Cultures of the throat were taken by means of sterile cotton-tipped swabs on all patients every day during their hospital course. The swabs were rubbed thoroughly over the posterior pharyngeal wall and the tonsils or tonsillar fossae, and were returned to the laboratory for bacteriological study within an hour.

Oral temperatures were taken at 4-hour intervals day and night, for the first three days and four times daily thereafter. Total and differential leucocyte counts were made daily on almost all patients. Blood cultures were made within a few hours of the time of hospital admission (usually at or near the time of the maximum recorded temperature) on 57 patients admitted on November 19 and 20. Urinalysis was done routinely on admission and on the fifth hospital day. Other procedures and examinations were carried out during the period of initial hospitalization in order to establish normal levels for the patients and in order to detect subsequent complications. These procedures are described in subsequent sections.

Clinical features

The clinical characteristics of the epidemic as observed in hospitalized patients were essentially similar to previous descriptions of this illness (1) (2). In general, the patients were mildly or moderately ill. Few had extremely high temperatures; few had septic complications; and the great majority experienced rapid symptomatic recovery.

Mode of onset. The illness began abruptly with feverishness, chilliness, malaise, and sore throat. Only a few had pre-existing respiratory symptoms. Three-fourths of the patients were admitted to the hospital within 48 hours of onset of the first symptom; nearly half were admitted within 24 hours of onset. Symptoms were at their maximum frequency at, or shortly after, the time of admission to the hospital.

Symptoms. In table 3 are listed the total frequency of various symptoms and physical signs. Feverishness was present in almost all patients while 90 per cent or more also had headache and chilliness. Very few patients had true shaking chills. Four-fifths of the patients complained of malaise and aching. Anorexia was complained of by the great majority of patients and half of them also had nausea or vomiting. Epistaxis occurred in more than one-third of all patients.

Sore throat (defined in this study as pain on swallowing) was noted by all patients. Only a few individuals, however, had severe local pain or great difficulty in swallowing. Nasal symptoms, such as stuffiness or discharge, occurred in a high proportion of patients. Cough and hoarseness, too, although not usually regarded as characteristic symptoms of this infection, occurred in half of the patients. Earache was complained of by 30 per cent of the patients; it was usually mild in degree and did not persist for more than a day.

Physical signs. The characteristic local physical signs in the throat, i.e., injection, edema, and exudate, were present in the great majority of cases. All gradations of severity were seen from "beefy" red, edematous mucous membranes studded with follicular exudate or covered with pseudo-membranes, to those which were only slightly inflamed. Exudate on either tonsillar tissue or pharynx was observed in almost all of the cases. Forty per cent had exudate of some extent on the posterior pharynx, usually small spots surmounting swollen lymphoid follicles. Ninety per cent of those patients with tonsillar tissue had exudate.

TABLE 3

*Frequency of Symptoms and Physical Signs in 89 Hospitalized Cases**

	TOTAL 89 CASES	SULFADIAZINE 49 CASES	NO SPECIFIC TREATMENT 40 CASES
	per cent	*per cent*	*per cent*
Symptoms			
Feverishness	99	98	100
Chilliness	89	87	90
Headache	95	96	95
Malaise	80	79	82
Anorexia	87	87	87
Sore Throat	100	100	100
Cough	47	50	44
Hoarseness	53	54	51
Nasal Symptoms	69	65	74
Earache	30	30	30
Epistaxis	37	33	42
Physical Signs			
Herpes labialis	29	29	30
Tender cervical lymph nodes	92	90	95
Injection of soft palate			
Present, any degree	94	92	98
Severe	70	69	70
Injection of pharynx			
Present, any degree	98	100	95
Severe	55	49	62
Injection of tonsillar tissue			
Present, any degree	100	100	100
Severe	89	87	92
Edema of uvula			
Present, any degree	89	90	88
Severe	53	61	42
Exudate on tonsillar tissue			
Present, any degree	92	89	94
Confluent	28	32	22
Exudate on pharynx	42	25	62

* Two patients who received only one dose of sulfadiazine omitted.

Tonsils were present in 58 of the patients; and tonsillar remnants (tags) in 23, while only 6 had complete absence of tonsillar tissue. As would be expected the extent of the exudate was related to the amount of tonsillar tissue present (table 4). Confluent exudate was found in a third of those with tonsils, in a tenth of those with only tonsillar tags, and in none of those without tonsillar tissue. In 87 patients in whom the maximum amount of exudate was recorded, it was described as confluent in 23, discrete (follicular) in 40, and pin-head in size in 18.

While the hyperemia of the mucous membranes had regressed by the end of the first ten days of illness, considerable injection was still present at the time of discharge of the patients from the hospital. This

TABLE 4

Relation of Tonsillar Tissue to Maximum Amount of Exudate

	MAXIMUM AMOUNT OF EXUDATE				TOTAL NUMBER OF CASES
	Confluent	Discrete	Pinhead	None	
Tonsils	21	26	9	2	58
Tonsillar "tags"	2	12	7	2	23
No tonsillar tissue	0	2	2	2	6
Total	23	40	18	6	87

fact was not fully appreciated until the patients were reexamined at a follow-up visit three weeks after onset, at which time the mucous membranes had regained their normal color.

Enlarged and tender lymph nodes in the anterior triangles of the neck were found in 90 per cent of patients, but in no instance was the swelling and tenderness such as to suggest a suppurative process. As the local abnormalities in the throat improved, the enlargement of the lymph nodes regressed, but a considerable number of patients still had enlarged nodes at the time of discharge from the hospital. At the three-week follow-up examination the normal state had been reached in most cases.

A few of the patients exhibited a diffuse erythematous blush of the skin at the time of admission to the hospital and coincident with their highest recorded temperatures. In all instances the blush subsided

rapidly and in no instance was it truly punctate or scarlatinal. Desquamation of the skin was not detected during the 10 day period of hospitalization or at the time of the three-week follow-up examination.

Temperature. The highest recorded temperature during the first 24 hours in the hospital is shown in table 5. One-third of the cases had a maximum temperature of 103° or more and 54 per cent had a maximum temperature of 102° or more. Only three patients were essentially afebrile throughout their hospital stay. With 3 exceptions the maximum recorded temperatures occurred during the first 24 hours in the

TABLE 5

Maximum Temperature During First Hospital Day

MAXIMUM TEMPERATURE	NO. CASES	PER CENT
105 or more	3	3.3
104–104.9	6	6.6
103–103.9	20	22.0
102–102.9	20	22.0
101–101.9	14	15.4
100–100.9	12	13.2
99– 99.9	13	14.3
less than 99	3	3.3
Total	91	100.0

hospital. Sulfadiazine treated cases have been included in this tabulation since specific therapy was begun at the time of, or shortly after, the occurrence of the maximum temperature.

Total and differential leucocyte counts. The average total leucocyte count on the first hospital day was 11,787; the average percentage of polymorphonuclear leucocytes at this time was 72 per cent. About half of the untreated patients continued to exhibit leucocytosis of 10,000 per cu.mm. or more throughout the first 10 days of illness. This finding was consistent with other evidences of continuing infection, such as persistence of type 5 streptococci in the throat, protracted low-grade hyperemia of the mucous membranes, and persistence of tender and enlarged cervical lymph nodes.

The occurrence of eosinophilia in the later stages of infectious diseases is well known. A slight tendency toward the development of

eosinophilia was also noted in the cases under study (table 6). The per cent of cases exhibiting more than 2 per cent eosinophils rose from no cases on the first two days of illness to 39 per cent of the cases on the sixth day of illness.

Effect of tonsillectomy on the course and severity of the illness. Among the group of forty-one patients not treated with sulfadiazine, twenty-one gave a history of tonsillectomy and twenty did not. Four of the tonsillectomized patients had no visible tonsillar tissue, while the remainder had tonsillar "tags" of varying size. An arbitrary division of patients according to a history of tonsillectomy yielded certain

TABLE 6

Daily Eosinophil Count in Untreated Patients

DAY OF ILLNESS	NO. COUNTS	AVE. % EOSINOPHILS	MORE THAN 2% EOSINOPHILS	
			Number	Per cent
1	10	0.3	0	0
2	10	0.7	0	0
3	18	1.4	2	11
4	29	1.9	8	28
5	32	1.9	12	38
6	38	2.3	15	39
7	36	1.9	11	31
8	30	1.8	9	30

differences which were of sufficient magnitude to warrant separate consideration of the two groups.

The daily frequency of symptoms in untreated tonsillectomized and non-tonsillectomized patients was essentially similar. In regard to local physical signs in the throat, some differences between tonsillectomized patients and those with tonsils were found, but these differences were not consistent or in one direction. For example, moderate or severe degrees of injection of the mucous membranes were more frequent in the tonsillectomized group, whereas edema of the uvula was more frequent in those whose tonsils were present. There was no obvious explanation for such differences apart from the fact that in considerable measure they were due to the small number of cases in each group. Other physical signs such as tender, enlarged cervical lymph nodes,

and the total frequency of exudate of any extent were similar in both groups. The daily frequency of type 5 streptococci, and the frequency of elevated leucocyte counts were also similar in tonsillectomized and unoperated patients.

A comparison was made of the daily temperature records in the two groups of untreated patients (fig. 3). The figure indicates, for each

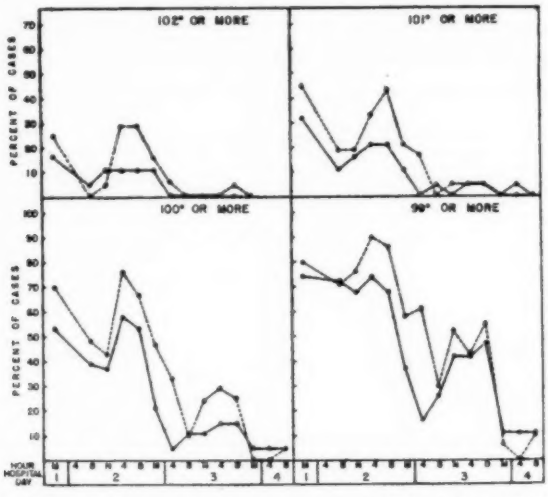


FIG. 3. PER CENT OF CASES WITH TEMPERATURES OF 99° OR MORE, 100° OR MORE, 101° OR MORE, AND 102° OR MORE AT SPECIFIED 4-HOUR PERIODS DURING HOSPITAL COURSE

Cases included in this figure received only symptomatic therapy. Solid lines indicate cases with tonsils present; dotted lines indicate cases with history of tonsillectomy.

time period, the per cent of patients who had an oral temperature of 99° or more, 100° or more, 101° or more, and 102° or more. Patients who had had tonsillectomy exhibited elevated temperatures more frequently than those whose tonsils were present. It was difficult to determine whether such differences were real, or were magnified by the small numbers of cases on which the comparison was based.

To study further the question of whether or not the severity of illness was related to the presence or absence of tonsils, comparisons

of various indices of severity were made between tonsillectomized and non-tonsillectomized patients. Sulfonamide treated patients were included in these comparisons because the criteria of severity were applied to data collected at the time of hospital admission and before the beginning of specific treatment. In brief, by such criteria of severity as maximum temperature of 102° or more, severe (3+) constitutional symptoms, severe (3+) injection of the mucous membranes, tender and enlarged cervical lymph nodes, initial total leucocyte counts of 12,000 per cu.mm. or more, and onset of illness before the evening of November 18, no differences of statistical significance were found between tonsillectomized and non-tonsillectomized patients. However, the frequency of confluent exudate and the frequency of predominant growth of streptococci in throat cultures taken early in the illness were significantly greater in patients with tonsils. These features are discussed elsewhere.

Summary. In general, the hospitalized patients were mildly or moderately ill. The illnesses began abruptly and the symptoms reached their maximum intensity within 48 hours of onset. Signs of inflammation in the pharynx, varying in severity, were present in all cases. Ninety per cent had exudate but in only 23 per cent was the exudate confluent. Half of the cases had moderate or severe degrees of edema of the uvula. More than half of the cases had a maximum temperature of 102° or more and only 3 were afebrile. The average total leucocyte count on the first hospital day was 11,787 per cu.mm. Slight eosinophilia, particularly after a week of illness, was common. Although almost all patients were symptomatically well after 10 days, local signs of inflammation, elevation of leucocyte counts, and enlargement and tenderness of cervical lymph nodes indicated the persistence of low-grade infection. In patients with a history of tonsillectomy the frequency and severity of symptoms and local physical signs was not modified to an important degree. Tonsillectomized patients, however, had more frequently elevated temperatures, and, as will be brought out in subsequent sections, exhibited other differences in regard to antibody response and the duration of the convalescent carrier state. These differences required that the history of tonsillectomy be considered in evaluating some of the possible effects of sulfadiazine therapy.

IV. EFFECT OF SULFADIAZINE ON CLINICAL ILLNESS

Selection of cases for treatment. Sulfadiazine was administered arbitrarily to hospitalized patients in alternate beds. Altogether 110 patients were included in the group in which sulfadiazine was alternately given and withheld; 53 had no specific treatment and 57 received sulfadiazine. Two of the latter were given only a single dose by error.

Included in the group of 110 were 19 patients who did not harbor type 5 streptococci in their throats. Some of these patients were members of other organizations and were already present on the wards when treatment was begun. Others were sent to the hospital from the affected regiment but were not cases or carriers of type 5 streptococci. Seven of the 19 were treated with sulfadiazine and 12 were not. The remaining 91 cases, of which 50 were treated and 41 were not, comprised the group on which the clinical studies were made. Two of the cases in the treated group received only one dose of the drug and were excluded from the therapeutic analysis. Two other cases were excluded from the analysis because the time of onset of illness was unknown. For most of the analyses to be presented 49 cases treated with sulfadiazine were compared with 40 cases who had only symptomatic therapy.

Specific and supportive treatment. Sulfadiazine was given orally in conventional dosage: 2 grams initially, followed by one gram every four hours, six times a day for five days. The total dosage was approximately 30 grams per patient. Sodium bicarbonate was given with each dose. Chemical determinations of the concentration of free sulfadiazine in the blood of the treated patients revealed levels of 5 to 15 mgs. per cent of free drug in every case.

All patients were treated by bed rest, a fluid intake of 3000 ml. or more daily, codeine when necessary in doses not exceeding one grain in eight hours, and saline throat irrigations twice or three times daily. Aspirin or other antipyretic drugs were not employed.

Effect of sulfadiazine on symptoms and physical signs. The daily prevalence of symptoms and physical signs were tabulated for the untreated group. The rates obtained were used as a basis for computing the expected prevalence in the treated group. On a given

day of treatment the number of patients under observation was composed of individuals who had been ill for varying periods of time. The "expected number positive" was arrived at by taking this variation into consideration and adjusting for it. The "expected proportion positive", then, was a rate adjusted for the length of illness.

The symptoms of feverishness, chilliness, and malaise showed small but consistent decreases in daily frequency in the treated group (fig. 4). The effect began promptly and was most evident after two days

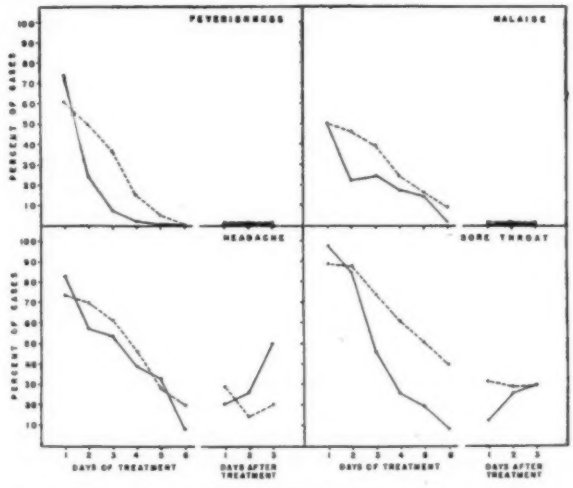


FIG. 4. DAILY FREQUENCY OF VARIOUS SYMPTOMS IN 49 CASES TREATED WITH SULFADIAZINE (SOLID LINES) AND IN 40 UNTREATED CASES (DOTTED LINES)

of treatment. After cessation of chemotherapy these symptoms did not recur. In contrast to other symptoms, the daily frequency of headache remained the same in treated and untreated patients. It is possible that the sulfadiazine group exhibited the composite result of two opposite effects, namely that the drug lessened the frequency of headache as a therapeutic effect in some patients and increased it, by virtue of its toxicity, in others.

The most impressive symptomatic result of sulfadiazine was its effect on the frequency of sore throat. By the end of three days of

treatment the drug had produced a 50 per cent reduction in this symptom as compared with the control group. The validity of this therapeutic effect was substantiated by the prompt return of the symptom to the control level two days after stopping treatment.

With one exception, the local physical signs in the throat, i.e., tender cervical lymph nodes, exudate on tonsils, palate, or pharynx,

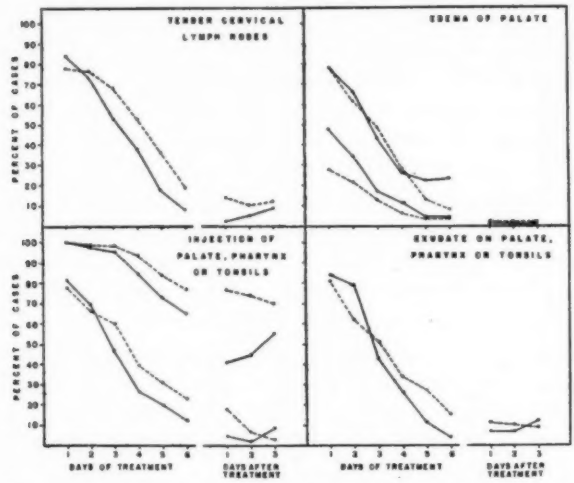

TENDER CERVICAL LYMPH NODES
EDEMA OF PALATE
INJECTION OF PALATE, PHARYNX OR TONSILS
EXUDATE ON PALATE, PHARYNX OR TONSILS
PERCENT OF CASES
DAYS OF TREATMENT
DAYS AFTER TREATMENT

FIG. 5. DAILY FREQUENCY OF VARIOUS PHYSICAL SIGNS IN 49 CASES TREATED WITH SULFADIAZINE (SOLID LINES) AND IN 40 UNTREATED CASES (DOTTED LINES)

Under "edema of palate" and "injection of palate, pharynx or tonsils" the upper sets of curves refer to the frequency of the physical signs of any intensity, and the lower sets of curves to severe degrees of the indicated signs.

and injection of the mucous membranes, all exhibited a consistent but minimal reduction in daily frequency in the treated group (fig. 5). Although the consistency of these differences lent support to their validity, the magnitude of the differences was not such as to suggest a clinically recognizable effect. Edema of the palate, although more frequent initially in the treated group, also decreased more rapidly in the treated than in untreated cases.

Effect of sulfadiazine on leucocytes. Sulfadiazine had a pronounced

depressant effect on the total leucocyte count and on the per cent of polymorphonuclear leucocytes (fig. 6). In this instance, it is difficult to distinguish between a therapeutic and a toxic effect of the drug, since either effect would have a similar result. However, it is unlikely that a toxic depression of the leucocytes would have occurred as rapidly as was observed in the treated group of cases. The late increase in elevated total and differential counts in both treated and untreated groups may have been due to the beginning of complications at this time.

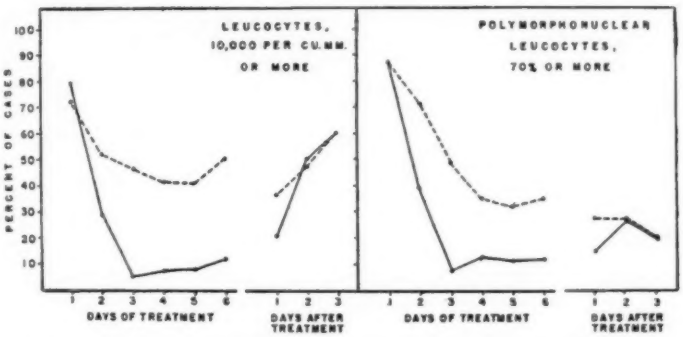

LEUCOCYTES, 10,000 PER CU.MM. OR MORE
POLYMORPHONUCLEAR LEUCOCYTES, 70% OR MORE
PERCENT OF CASES
DAYS OF TREATMENT
DAYS AFTER TREATMENT

FIG. 6. DAILY FREQUENCY OF TOTAL LEUCOCYTE COUNTS OF 10,000 PER CU. MM. OR MORE AND OF DIFFERENTIAL COUNTS WITH 70 PER CENT OR MORE OF POLYMORPHONUCLEAR LEUCOCYTES IN 49 CASES TREATED WITH SULFADIAZINE (SOLID LINES) AND IN 40 UNTREATED CASES (DOTTED LINES)

Effect of sulfadiazine on the persistence of type 5 streptococci. The effect of sulfadiazine on the daily prevalence of type 5 streptococci was sharp but transitory (fig. 7). In the untreated group, the organisms were recovered in more than 90 per cent of patients every day during the entire period of hospitalization; in the treated group the prevalence rate of type 5 streptococci was reduced quickly to 55 per cent and was maintained at this level for the duration of treatment. The number of colonies of β-hemolytic streptococci recovered on blood agar plates was also greatly decreased in the treated group. Within three days after sulfadiazine was discontinued, type 5 streptococci were again found in 95 per cent of the cases. It is obvious that sulfadiazine suppressed but did not eradicate the organisms.

It so reduced their numbers that in many cases they were no longer detectable by culture. Sufficient numbers of them persisted, however, so that multiplication took place rapidly as soon as the inhibitory influence of the drug was removed. The media on which the culture swabs were streaked contained sufficient para aminobenzoic acid to overcome the inhibitory effect of sulfadiazine on the growth of the streptococci (3).

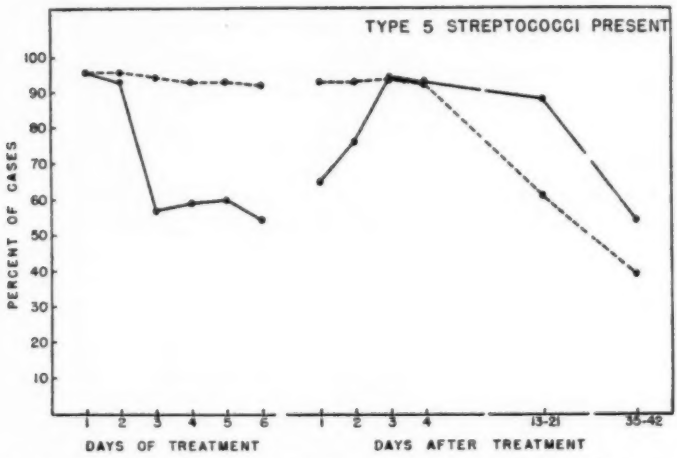


FIG. 7. FREQUENCY OF TYPE 5 STREPTOCOCCI IN DAILY THROAT CULTURES

Solid line represents cases treated with sulfadiazine; dotted line, cases not receiving specific treatment.

Effect of sulfadiazine on temperature. An alteration in the febrile course might be expected to afford as objective a measurement as possible of the therapeutic effect of sulfadiazine. The comparison was made between 40 untreated patients and 43 patients whose treatment was begun between 8 p.m. of the first hospital day and 4 a.m. of the second hospital day (fig. 8). Six patients whose treatment was begun before or after this time period were not included.

Sulfadiazine appeared to effect a considerable reduction in the frequency of elevated temperatures. This effect was most notable during the second and third day of treatment during which time the

expected afternoon rise in temperature was greatly reduced in the treated group.

Effect of sulfadiazine as influenced by the presence or absence of tonsils. In a previous section it was indicated that patients with a history of tonsillectomy differed in certain respects from those whose tonsils

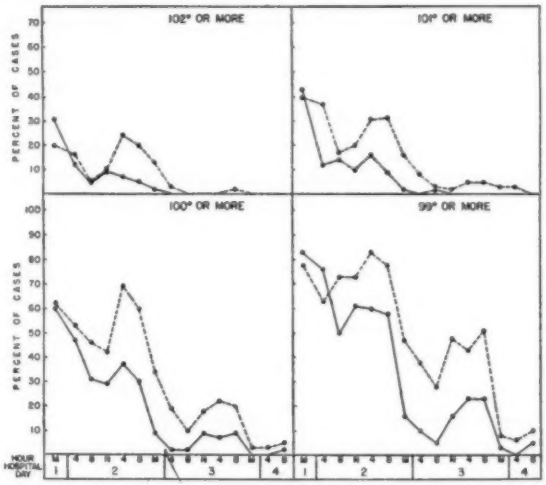


FIG. 8. PER CENT OF CASES WITH TEMPERATURES OF 99° OR MORE, 100° OR MORE, 101° OR MORE, AND 102° OR MORE AT SPECIFIED 4-HOUR PERIODS DURING HOSPITAL COURSE

Solid lines indicate temperatures of 43 cases treated with sulfadiazine; dotted lines, 40 cases receiving only symptomatic therapy.

had not been removed. In the group of untreated patients approximately half had their tonsils removed and half did not. Among the treated patients, however, only six had tonsillectomy and 40 did not.

Two questions were raised by the unequal distribution of tonsillectomized patients in the treated and untreated groups: 1) did bias enter into the selection of cases for treatment, and 2) were the effects of sulfadiazine real or were they due to the type of case treated, i.e., tonsils not removed?

It cannot be denied that bias did enter into the selection of patients for treatment although the manner in which it may have occurred was

not evident either at the time of selection, or in retrospect. If selection for treatment on the basis of supposed severity had occurred, it is probable that the size of the tonsils, the extent of the exudate, and the degree of edema of the uvula would have been determining factors since all of these were more marked in patients with tonsils than in those who had tonsillectomy. However it was impossible to demonstrate that the treated patients were initially more severely ill than the untreated patients. The frequency of symptoms and physical signs was the same in both groups (table 3). The number of patients with a maximum temperature of 103° or more (before sulfadiazine was begun) was slightly greater in the untreated than in the treated group. With regard to such criteria of severity as the intensity of symptoms, and the height of the leucocyte count, moreover, the untreated patients, and in particular, those with a history of tonsillectomy, were as severely ill as the treated patients.

The second question raised by the unequal distribution of tonsillectomized patients in treated and untreated groups was whether or not effects which might be assumed to be the result of sulfadiazine treatment could have been, in reality, differences in response to infection between patients with and without tonsils.

It was stated in a previous section that important differences did not exist between untreated patients, with and without tonsils, with regard to the frequency and severity of symptoms, physical signs, and clinical laboratory findings.

The conclusions already drawn in regard to the effect of sulfadiazine on symptoms, physical signs, leucocyte counts, and frequency of type 5 streptococci in throat cultures therefore appeared to be valid, regardless of differences in the distribution of tonsillectomized patients in the treated and untreated groups.

With regard to the temperature curves however it was found necessary to consider the previous history of tonsillectomy in evaluating the therapeutic effect of sulfadiazine. A comparison of the daily temperature records of untreated patients divided into those with tonsils and those with tonsillectomy showed that tonsillectomized patients had somewhat more fever than those with tonsils (fig. 3). In considerable measure, these differences may have arisen because of the small numbers of cases. A comparison of figure 3 and figure

8 leads to the conclusion that, in the latter figure, the favorable effects of sulfadiazine were magnified unduly by the generally higher temperatures of untreated tonsillectomized patients. If the comparison is limited to treated patients with tonsils and untreated patients with tonsils, the therapeutic effect of sulfadiazine is reduced to very modest proportions indeed, although it is still discernible.

Summary. Sulfadiazine was administered in usual therapeutic doses to alternate patients with type 5 streptococcal infection. There was a considerable decrease in the daily prevalence of sore throat in the treated group but impressive effects on other symptoms were not obtained. Sulfadiazine did not appear to hasten the improvement of local signs of inflammation. Chemotherapy had a pronounced depressant effect on total and differential leucocyte counts and on the prevalence of type 5 streptococci recovered in throat cultures. Both of these effects, however, were transitory and persisted only during the period of treatment.

An unequal distribution of cases with a history of tonsillectomy was found in the treated and untreated groups, indicating possible bias in the selection of patients for treatment. This selection did not appear to affect the comparability of treated and untreated groups in regard to the severity of illness. However, the apparent effect of sulfadiazine in reducing elevated temperatures was in some measure the result of the unequal distribution of patients with and without tonsils in the treated group.

V. COMPLICATIONS

An usual opportunity was afforded to make detailed observations on the incidence and character of complications, with special reference to the development of late non-suppurative sequelae. These studies were carried out in all hospitalized cases with type 5 streptococcus infections, both primary and secondary, totalling 100. No detailed studies were made on asymptomatic carriers.

Methods

During the initial period of hospitalization, all patients were examined carefully for evidences of cardiac abnormalities, arthralgia, skin rashes, or other symptoms and signs suggestive of rheumatic

fever. Roentgenograms of the chest were taken soon after admission to the hospital and again 6 or 7 days later. Blood pressure was determined at least three times in the supine resting position during the first week of illness. Roentgenograms of the paranasal sinuses were were made on all patients who complained of any symptom which might be attributed to infection of these structures, and also on patients who had persistent or unexplained fever. Electrocardiograms employing three standard leads and the IV-F chest lead were taken on patients during the first week of illness; the recordings were made with the patients supine and at rest. At least two urinalyses were made on all patients during the hospital stay.

Three weeks after the clinical onset of the epidemic, on December 9 and 10, all of the hospitalized patients were re-examined. At this time, an interval history was taken, physical examination made, blood pressure determined, urinalysis performed, and another electrocardiogram taken.

Six weeks after the epidemic, during the first week in January, the patients were again examined and similar studies carried out.

Suppurative complications

Only two cases had frankly suppurative local complications. One patient entered the hospital with signs of inflammation of the throat of mild degree. The infection rapidly became worse until a well-defined peritonsillar abscess (from which type 5 streptococci were obtained) was incised and drained 10 days after onset. Sulfadiazine was not administered in this case. Another pateint had evidence of mild streptococcal pharyngitis until the sixth day of illness when the temperature rose, pain in the face and jaws developed and purulent material was found in both antra. No chemotherapy was given. A third patient had a recurrence of exudative tonsillitis:

Case T-235. A 23 year old soldier became ill on November 19 and was hospitalized the next day. His temperature on admission was 105° and he exhibited the local signs of severe streptococcal tonsillitis. Sulfadiazine was administered for 5 days with prompt subsidence of the febrile reaction and gradual clearing of the tonsillar inflammation. Three days after cessation of specific therapy, on December 1, the temperature rose to 102°, and there was a recurrence of sore throat and local signs of tonsillar infection. Type 5 streptococci were again recovered

from throat cultures made at this time. The second illness subsided promptly without specific treatment.

Several other patients had some degree of recurrence of sore throat after discharge from the hospital but were not readmitted to the hospital because of this.

No other septic or localized complications were discovered. Specifically, no patient developed pneumonia, otitis media, or suppurative lymphadenitis. Blood cultures obtained on 57 patients shortly after admission to the hospital were sterile.

Non-suppurative complications

Thirteen patients exhibited clinical or laboratory evidence of non-suppurative late sequelae. These have been classified as follows: 1. Acute rheumatic fever (3 cases); 2. Possible rheumatic fever (2 cases); 3. Asymptomatic individuals with transient electrocardiographic abnormalities (4 cases); 4. Unexplained, persistent fever (4 cases). In addition, one patient experienced an exacerbation of chronic nephritis and a number of others had microscopic hematuria and other urinary abnormalities.

Acute rheumatic fever. Three patients exhibited signs, symptoms, and laboratory findings sufficient to establish clearly the diagnosis of acute rheumatic fever.

1. Case T-227. An 18 year old soldier complained of a sore throat on November 15 and was admitted to the hospital on November 19 with a temperature of 102° and moderately severe acute follicular tonsillitis. He received sulfadiazine for five days, experiencing a rapid subsidence of fever and progressive clearing of the signs of local inflammation. At the routine follow-up examination on December 10, he was found to have cardiac arrhythmia and painful swollen ankles and elbows which were first noticed 18 days after the onset of sore throat. Electrocardiogram at this time revealed second degree heart block with Wenkebach's periodicity (Fig. 9). A previous tracing had been normal. No cardiac murmurs were detected. The erythrocyte sedimentation rate was elevated (0.5 mm. per min., Rourke-Erstine method).

2. Case T-273. A 19 year old soldier developed streptococcal tonsillitis on November 18 and was admitted to the hospital two days later with a temperature of 103°. Concomitant with the administration of sulfadiazine, fever and local inflammation subsided rapidly, and he was asymptomatic when discharged from the hospital. On December 12 he was readmitted having experienced feverishness, and multiple joint pains for five days. He was found to have acutely painful

and swollen knees, ankles, and toes, as well as painful shoulders. A well marked skin eruption typical of erythema marginatum was present. There were no cardiac murmurs. Electrocardiographic tracings, which had previously been normal, showed first degree heart block with a P-R interval of 0.25 seconds. The erythrocyte sedimentation rate was elevated above normal (1.5 mm. per min.).

3. Case T-289. A 19 year old soldier developed symptoms of streptococcal pharyngitis of moderate severity on November 19 and was admitted to the hospital two days later with a temperature of 102°. Without specific therapy, the local infection subsided in the course of a few days. On December 17 he was readmitted to the hospital, having had an onset of symptoms 25 days after the beginning of the infection. He complained of feverishness and pain in feet, ankles, knees, elbows, and shoulders and in the hospital was observed to have

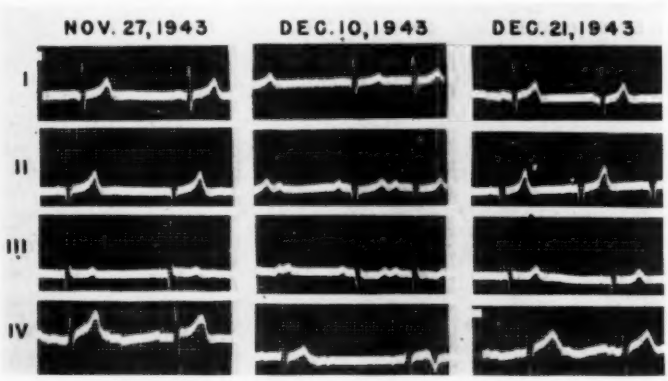


FIG. 9. CASE T 227. ACUTE RHEUMATIC FEVER

migrating polyarthritis. A loud apical systolic murmur, which had not been present during the initial illness, developed under observation. Serial electrocardiographic tracings showed a P-R interval which increased from 0.16 seconds to 0.20 seconds (Fig. 10). The erythrocyte sedimentation rate was elevated (0.8 mm. per min.).

All three patients had prolonged, low-grade fever. Their arthritic symptoms were improved by salicylate medication. After prolonged bed rest at this hospital, they were transferred to general hospitals for convalescent care.

Possible acute rheumatic fever. Two patients had symptoms or laboratory findings suggesting the possible presence of rheumatic fever but in these cases a definite diagnosis was not established.

1. Case T-317. This 19 year old soldier developed symptoms charateristic of streptococcal pharyngitis on November 27 (secondary case) and was hospitalized on November 29. The physical signs and maximum temperature (102°) were indicative of a moderately severe illness. Sulfonamide drugs were not administered. The febrile course of the initial illness was rather prolonged and a normal temperature was not recorded until the 10th day of illness. On the 14th day fever recurred and persisted for another 10 days. During this second febrile period the patient complained of protracted headaches, epistaxis, and nasal obstruction. There was no evidence of acute suppurative sinusitis but roentgenograms showed thickening of the mucous membranes of both antra. There were no joint pains or clinical cardiac abnormalities. The erythrocyte sedimentation rate was at the upper limit of the normal range (0.4 mm. per min.). An electro-

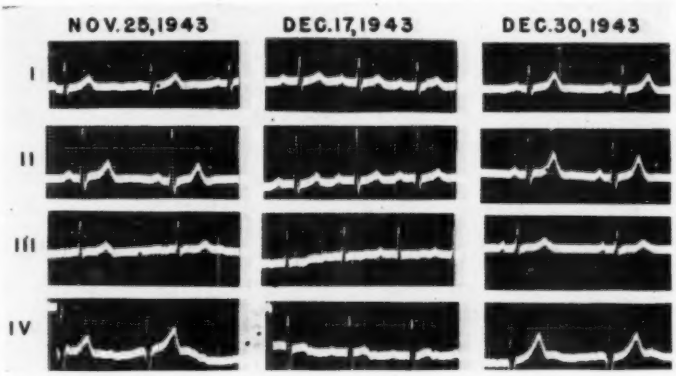


FIG. 10. CASE T 289. ACUTE RHEUMATIC FEVER

cardiographic tracing taken 21 days after the onset of the illness (December 17) showed sharply inverted T waves in leads II and III (Fig. 11); 41 days after onset (January 7), T_2 was less sharply inverted, and 87 days after onset (February 22) T_2 had become diphasic. The diagnosis of rheumatic fever in this patient was suggested on the basis of prolonged (and otherwise unexplained) fever and electrocardiographic changes.

2. Case T-280. An 18 year old soldier developed a sore throat on November 19 and was hospitalized with evidence of rather mild streptococcal tonsillitis. During the first week of illness, the temperature was not above 99.4°. On the 10th day of illness, the temperature rose to 100° and thereafter for 26 days remained irregularly elevated, with almost daily maximum recordings of 101°. The patient was then discharged from the hospital but returned on January 5 (47 days after the onset of the initial illness) with a temperature of 102°. On this occasion, he became afebrile and asymptomatic in 8 days. During the whole period, beginning a week after the original illness, he complained of weakness, headache,

precordial oppression, and joint pains, especially in the elbows and wrists. On several occasions these joints were objectively mildly red, warm, and swollen. Exhaustive laboratory studies including numerous electrocardiographic records leucocyte counts, erythrocyte sedimentation rates, and roentgenograms of chest and paranasal sinuses revealed no definite abnormalities. The tentative diagnosis of acute rheumatic fever was suggested on the basis of prolonged fever and both subjective and objective evidences of polyarthritis.

Both of these patients were eventually returned to duty.

Asymptomatic electrocardiographic changes. Four other patients exhibited transitory T-wave and other electrocardiographic changes sufficiently abnormal to suggest the possibility of acute myocarditis. The

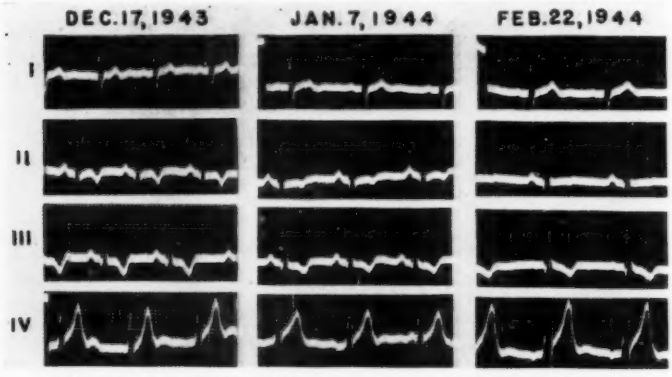


FIG. 11. CASE T 317. SUSPECTED ACUTE RHEUMATIC FEVER

time interval after the onset of streptococcal pharyngitis during which these changes took place suggested that their pathological basis may have been rheumatic myocarditis. None of these patients had symptoms suggestive of acute rheumatic fever and none had cardiac murmurs or other abnormalities detectable by clinical examination. Erythrocyte sedimentation rates, leucocyte counts, and temperature records were not made subsequent to their discharge from the hospital after recovery from the initial illness. One patient (T-272) gave a history of a previous attack of rheumatic fever six years before. The electrocardiographic records are summarized as follows:

1. Case T-207 (Fig. 12): 7 days after onset (Nov. 27)—T_1 and T_4 diphasic; T_2 and T_3 inverted

22 days after onset (Dec. 10)—T_1 diphasic; T_2, T_3, and T_4 sharply inverted
96 days after onset (Feb. 22)—T_1, T_2, T_3, and T_4 upright

2. Case T-237 (Fig. 13): 9 days after onset (Nov. 27)—T_1 and T_4 upright; T_2 and T_3 inverted
22 days after onset (Dec. 10)—T_1, T_2, and T_4 upright; T_3 inverted
43 days after onset (Dec. 31)—No change

3. Case T-265 (Fig. 14): 6 days after onset (Nov. 24)—T_1, T_2, and T_4 upright; T_3 inverted
22 days after onset (Dec. 10)—No change
50 days after onset (Jan. 7)—T_1 upright; T_2 and T_3 inverted; T_4 diphasic
96 days after onset (Feb. 22)—T_1 and T_4 upright; T_2 diphasic; T_3 inverted

4. Case T-272 (Fig. 15): 7 days after onset (Nov. 25)—P-R 0.15 sec.; T_1, T_2, and T_4 upright; T_3 diphasic
22 days after onset (Dec. 10)—P-R 0.20 sec.; T_1 and T_4 upright; T_2 and T_3 inverted
33 days after onset (Dec. 21)—P-R 0.17 sec., T_1, T_2, and T_4 upright; T_3 inverted
50 days after onset (Jan. 7)—P-R 0.15 sec.; T_1, T_2, and T_4 upright; T_3 diphasic

Recurrence of fever without localizing signs. Four patients were readmitted to the hospital after subsidence of the initial illness and exhibited unexplained fever for periods varying from 6 days to 4 weeks.

1. Case T-283. A 19 year old soldier developed rather severe streptococcal tonsillitis on November 18. His temperature on admission to the hospital was 102.6°. Sulfadiazine was administered for five days during which time the temperature returned rapidly to normal while the signs of inflammation in the throat regressed slowly. Eleven days after the onset of the initial illness, the patient returned to the hospital complaining of feverishness and sore throat, but there was little objective evidence of local pharyngeal reaction. During the following two weeks, the temperature was persistently elevated, often to 102°. He complained only of headache and lethargy and physical examination yielded normal findings. The highest total leucocyte count during this period was 10,000 cells per cu. mm. All other laboratory studies, including electrocardiograms, roentgenograms of chest and paranasal sinuses, and erythrocyte sedimentation rates were normal.

2. Case T-217. A 23 year old soldier was admitted to the hospital with tonsillitis on November 19, with symptoms present for one day. The initial illness

was rather mild; the admission temperature was 102° but remained below 99° after the second hospital day. Sulfadiazine was administered for five days. On December 1 (13 days after onset), he again felt feverish and was readmitted to the

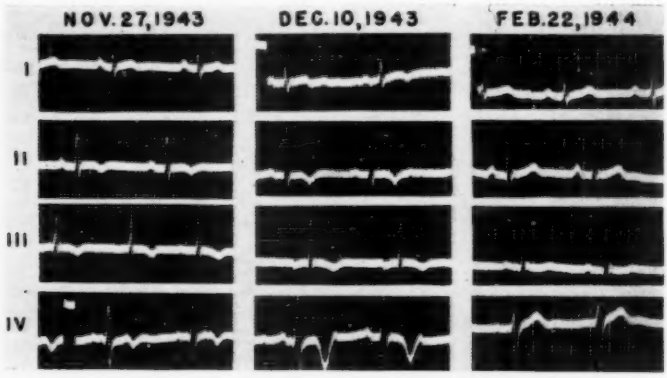


FIG. 12. CASE T 207. ASYMPTOMATIC

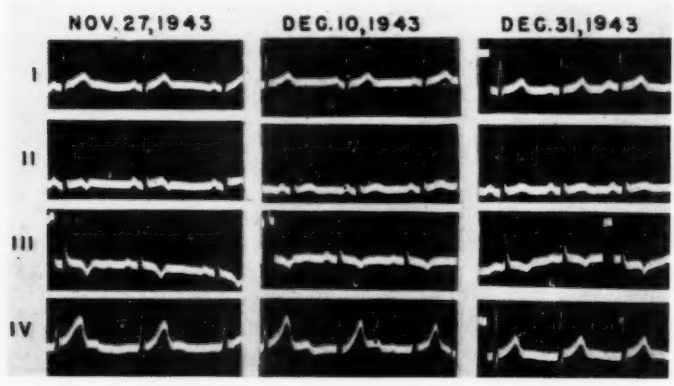


FIG. 13. CASE T 237. ASYMPTOMATIC

hospital. For the next four weeks the patient continued to have fever intermittently as high as 102.4°. There were no objective physical findings and he complained only of fatigue, listlessness, and malaise. All laboratory studies were within the normal limits except the leucocyte count which was elevated to a maximum of 17,500 cells per cu. mm.

3. Case T-236. An 18 year old soldier was hospitalized on November 20 with symptoms of tonsillitis for two days. Although the appearance of the throat suggested a mild infection, the admission temperature was 104.2°. A normal temperature was reached on the fourth hospital day. The patient was readmitted

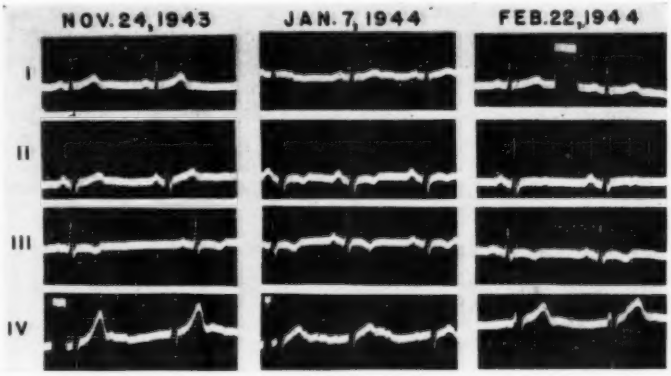


FIG. 14. CASE T 265. ASYMPTOMATIC

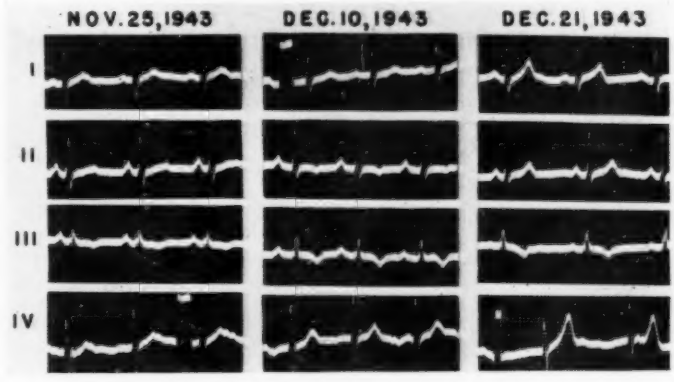


FIG. 15. CASE T 272. ASYMPTOMATIC

to the hospital on December 1 (12 days after onset of the original illness) complaining of feverishness, sore throat, and abdominal discomfort. The appearance of the throat was essentially normal and there were no other abnormal physical findings. Nevertheless, he exhibited low-grade fever (between 99° and 100°) for the next 12 days. He complained at times of joint pains but no objective evi-

dence of arthritis was detected. Roentgenograms of the paranasal sinuses indicated involvement of these structures but related symptoms or physical signs could not be elicited. All other laboratory procedures yielded normal findings.

4. Case T-264. This 29 year old soldier became ill on November 19. The initial illness was mild with a maximum temperature of 100.2° and signs indicative of relatively slight inflammation in the throat. The temperature was normal by the third day of illness. On December 2, 12 days after the onset of the initial illness, he was readmitted, complaining of feverishness, malaise and sore throat for one day. The patient was febrile for the next 6 days during which time intensive physical and laboratory examinations revealed no abnormal findings.

These four patients all experienced febrile relapses varying in duration from one to four weeks following an initial attack of streptococcal pharyngitis or tonsillitis. No adequate explanation for the fever was obtained. They may have represented instances of low-grade lymphadenitis or lymphangitis and for want of a better term are classified as non-suppurative "streptococcal fever."

Renal complications. No instances of acute glomerulonephritis were encountered but a number of patients had microscopic hematuria and other urinary abnormalities during the early febrile stages of illness. One patient had an exacerbation of chronic nephritis:

Case T-216. Twenty-four hours after the onset of a severe attack of tonsillitis caused by β-hemolytic streptococcus, type 5, the patient was observed to pass grossly bloody urine. Although the patient was treated with sulfadiazine the hematuria occurred before the first dose of drug was administered. A history was elicited of previous episodes of hematuria associated with sore throats. Microscopic hematuria, albuminuria and casts were still present 8 weeks after onset at which time the patient was transferred to another hospital for further care. In contrast to the usual 2 to 3 weeks interval between streptococcal infection and onset of acute nephritis, this instance of probable exacerbation of chronic nephritis occurred immediately after the onset of the streptotoccal infection.

Among the group of patients not treated with sulfadiazine, 19 per cent had microscopic hematuria and 27 per cent had albuminuria during the period of hospitalization or at the three and six weeks follow-up examinations. One patient, in one urine specimen had "many" red blood cells. In all other instances the hematuria consisted of only "rare" red blood cells in the centrifuged sediment. Rare casts were found in the urine in 15 per cent of the patients. The maximum frequency of occurrence of microscopic hematuria

coincided with the height of fever in most instances and occurred in the initial urine specimen obtained after admission to the hospital. Edema, hypertension and other signs or symptoms suggesting nephritis were not found.

In the patients treated with sulfadiazine a similar frequency of hematuria, albuminuria, and cylindruria was encountered. These abnormalities were also most common during the initial period of hospitalization. In view of the administration of sulfadiazine in this group, it was impossible to distinguish between abnormalities that could have resulted from the immediate or delayed effects of the streptococcal infection and those resulting from chemotherapy.

Hospital cross-infections. Observations were made on the spread of type 5 streptococci to other patients and hospital personnel in contact with the cases of type 5 streptococcus infection. As was mentioned in a previous section, 19 patients with respiratory disease, but not harboring type 5 streptococci when admitted to the hospital, were housed on the study wards. These 19 patients were in close proximity to patients with type 5 streptococcus infections for periods of from 5 to 10 days, in an environment in which it is likely that the air, floors, and bedding were contaminated with type 5 streptococci (4). From 7 to 10 daily throat cultures were obtained from these patients during their hospitalization, the initial cultures being taken from November 19 to November 26.

Four of the 19 acquired type 5 streptococci during their hospital stay. All four had from 4 to 10 negative daily throat cultures before acquiring the organisms. Two of the subjects had only a single culture positive for type 5 streptococci, one had 2 positive cultures, while the fourth patient remained a carrier of type 5 streptococci for a month. In addition, one other individual had no type 5 organisms in 10 daily cultures but on December 20 (one month after the onset of the epidemic) became ill with type 5 streptococcus sore throat. In summary, on an open ward in which the majority of the patients harbored type 5 streptococci, only 4 out of 19 persons not already infected acquired the organisms. All of the 4 became "healthy" carriers and in 3 of the 4 the carrier state was transient.

Additional observations on cross-infection were made on the professional and housekeeping personnel of the study wards. Throat

cultures were obtained during the course of the epidemic—mostly on November 24, 25, and 26—from 8 doctors, 2 nurses, and 10 enlisted corpsmen, all of whom were in more or less intimate contact with the patients. Most of these 20 persons had a single throat culture. Only one individual, a physician who examined some of the patients daily for 3 days, acquired type 5 streptococci and noted soreness of the throat.

Influenza. The occurrence of an epidemic of respiratory disease due to influenza virus A shortly after the streptococcus epidemic afforded an unusual opportunity to study the relationship of the two

TABLE 7

*Serological Response to Influenza Virus A**

	NUMBER TESTED	RISE IN TITER FOR INFLUENZA	
		Number	Per cent
Type 5 Streptococci not present			
H Co.	117	31	26
G and Hq. Co.	71	17	24
Type 5 Streptococci present			
Primary cases	84	14	17
Secondary cases	15	1	7
Carriers	27	5	19

* Based on rise in titer of 2 or more dilution increments in agglutination-inhibition test between acute and convalescent sera.

diseases. In the group under study (Companies G, Hq, and H) the diagnosis of influenza was made on the basis of the red cell agglutination-inhibition reaction (5). The cases occurred during a two-week period beginning approximately three weeks after the onset of the streptococcus outbreak. A detailed presentation of the data obtained during the influenza epidemic will be made in another report. Here it is of interest to point out that the attack rate for influenza was approximately the same for those who had recovered from type 5 streptococcus infection, for healthy carriers of type 5 streptococci, and for those who had never acquired the type 5 organisms (table 7). Hospitalized cases were mildly or moderately ill and exhibited a clinical pattern similar to that observed in patients from other or-

ganizations on the Post. No instance of streptococcal pneumonia occurred despite the fact that a number of patients with influenza still harbored type 5 streptococci.

Summary. Suppurative complications resulting from type 5 streptococcal infection were few in number. One patient developed a peritonsillar abscess and another had purulent maxillary sinusitis. A third patient suffered a recurrence of exudative tonsillitis.

Non-suppurative complications were more numerous. Three cases of acute rheumatic fever, all with polyarthritis and carditis, were detected 18, 20, and 25 days, respectively, after the onset of streptococcal infection. Two other individuals had febrile relapses with symptoms suggestive of rheumatic fever but a definite diagnosis could not be made. Four subjects had febrile relapses varying from 1 to 4 weeks in duration without specific localizing symptoms or physical signs. Four other individuals who were asymptomatic were found to exhibit transient electrocardiographic changes during convalescence.

One patient experienced a recrudescence of chronic nephritis. Minor urinary abnormalities were detected in a number of other patients, chiefly during the febrile period.

Spread of type 5 streptococci occurred among other patients on the same wards as the cases of type 5 pharyngitis and among professional personnel caring for the patients. With one exception, these secondary infections were asymptomatic.

An epidemic of influenza occurred about 3 weeks after the beginning of the streptococcal outbreak. Influenza virus A infection occurred with no greater frequency and with no greater severity among subjects who harbored type 5 streptococci than among those who remained free from streptococcal infection.

VI. IMMUNOLOGICAL AND OTHER LABORATORY STUDIES

Methods

Blood specimens were obtained on November 20 or 21 on all enlisted men belonging to the two affected companies (Hq and G) of the regiment, whether hospitalized or not, and the unaffected control company (H). With few exceptions, these acute phase specimens

were collected within 3 or 4 days of the time of probable initial infection. Hospitalized patients were bled again on the day of discharge (approximately 10 days after the onset of illness). Three weeks after the beginning of the outbreak, on December 9 and 10, blood specimens were again obtained from all members of Hq and G Companies. Six weeks after the outbreak, on December 31 and in the following week, the great majority of all individuals in both affected and control companies were again bled. The blood samples were collected in a manner which insured sterility, were allowed to clot, and the serum removed and stored at 4°C.

Throat culture swabs were plated on the surface of blood agar plates made with a meat infusion base containing 7 per cent of horse blood and 5 mgs. per cent of para-aminobenzoic acid. The swabs were rubbed thoroughly over a small portion of the plate and the inoculum spread over the remaining surface of the plate with a sterile wire needle. Plates were incubated at 37°C. for 24 hours.

Estimates of the number of colonies of streptococci on each plate were made. The organisms were described as "predominant" if more than half of all the colonies (of any kind) on the plate were β-hemolytic streptococci. When less than this proportion of all colonies were β-hemolytic streptococci, they were listed as merely "present". Hemolytic colonies were picked with the aid of a colony microscope, and transferred to blood agar slants. After incubation, the slants were stored in the cold to await serological identification.

Bacterial extracts were prepared by Lancefield's method from the growth of organisms in 40 ml. of broth. Grouping and typing were performed by the capillary-tube method of Swift, Wilson, and Lancefield (6).[3] Commercial grouping sera (Lederle) were used. Serological identification was completed within a few weeks after the organisms were isolated on blood agar slants. Representative strains were preserved in the frozen and dried state for subsequent studies.

Antistreptolysin titers were determined by a modification of the method of Hodge and Swift (7).

Antifibrinolysin titers were determined by a quantitative method developed in this laboratory and previously described (8).

[3] Generous supplies of M-precipitin typing sera were made available through the kindness of Drs. Swift and Lancefield.

Serological reactions with pneumococcus C substance (9) were tested on non-lipemic sera, after clarification by centrifuging. Pneumococcus C substance[4] was used in a final dilution of 1:40,000.

In the following tables, antistreptolysin and antifibrinolysin responses are presented as the maximum rise from the initial level in terms of dilution increments (number of tubes). In no instance was the maximum titer obtained in the 10-day specimen. Hence, both hospitalized and non-hospitalized subjects from the two affected companies were alike in having for comparison with the acute phase specimen two specimens during convalescence: one at 3 weeks, the other 6 weeks after the beginning of the epidemic.

Antistreptolysin

The results of antistreptolysin determinations are presented in table 8. In brief, 80 per cent of all hospitalized cases with type 5 streptococcus infection had a significant (two-tube) rise in titer, and 31 per cent of all carriers had a significant rise in titer.

Since epidemiological evidence indicated that this was a food-borne epidemic, it is probable that the route of infection (and possibly the amount of the infectious inoculum) differed in primary and secondary cases. In the latter, the infection was presumably acquired by air contamination (10) or direct contact with primary cases or carriers. Although somewhat fewer secondary cases had a two-tube rise in antistreptolysin than primary cases, the number of secondary cases was small and the differences in antibody response were probably not important. In this study, the antibody response appeared to be the same among early and late cases despite possible differences in route of infection and dose of inoculum.

Cases and carriers differed in their antistreptolysin response; more than twice as many cases as carriers had significant increases in these antibodies. The precise nature of the carrier state is unknown. The group of carriers in this study probably included some individuals who were ill but did not receive medical care in either dispensary or hospital. This is especially likely since the epidemic occurred in an organization of paratroopers in whom "toughness" was a cultivated attribute. Since approximately one-third of "healthy" carriers had

[4] Kindly supplied by Dr. Walther F. Goebel.

a significant rise in antistreptolysin, the conclusion seems inescapable that a proportion of "healthy" carriers did have "disease".

Only one individual in the control (H) company and in the unaffected soldiers in G and Hq Companies had a two-tube rise in antistreptolysin. Approximately 40 per cent of all individuals in these

TABLE 8

Antistreptolysin Response

	NUMBER TESTED	ACUTE PHASE SERA AVERAGE TITER*	CONVALESCENT PHASE SERA, MAXIMUM CHANGE IN TITER IN DILUTION INCREMENTS					
			0 or decrease		+1		+2 or more	
			No.	Per cent	No.	Per cent	No.	Per cent
Type 5 streptococci not present								
G and Hq. Co.	98	187	86	88	12	12	0	0
H Co.	118	202	106	90	11	9	1	1
Total	216	195	192	89	23	11	1	0
Type 5 streptococci present								
All hospitalized cases	100	191	8	8	12	12	80	80
All cases	112†	191	12	11	14	12	86	77
Primary	89	190	5	6	12	13	72	81
Early Secondary	11	172	2	18	0	0	9	82
Late Secondary	10	213	5	50	0	0	5	50
All "healthy" carriers	32‡	208	15	47	7	22	10	31
Primary	9	171	1	11	6	67	2	22
Early Secondary	13	231	7	54	1	8	5	38
Late Secondary	9	222	6	67	0	0	3	33

* Geometric average.

† Includes 2 cases not classified as primary or secondary.

‡ Includes 1 carrier not classified as primary or secondary.

two companies harbored β-hemolytic streptococci (other than type 5) at some time during the six weeks period of culturing. At least 4 cultures were obtained from each man. Twenty-three individuals (11 per cent) harbored Group A strains other than type 5. None of these subjects was hospitalized with a respiratory illness resembling streptococcal pharyngitis and none of them had a two-tube rise in antistreptolysin. (The one significant increase in titer occurred in a

soldier who had no clinical illness but harbored a Group C streptococcus.) These observations confirm the specificity of the antistreptolysin test and also indicate that the carrier state does not necessarily, or even generally, result in an antibody response. Such a response may be conditioned by the type or strain, by the size of the inoculum, or by the host factor of initial immunity status.

Experimental (11) and clinical (12) evidence indicates that antistreptolysin is an indicator of previous experience with β-hemolytic streptococci but is not a measure of specific immunity. Additional clinical confirmation is to be found in the results of the present study. If this antibody were a measure of immunity, one would expect non-infected individuals to have higher initial titers than infected subjects, and carriers to have higher initial levels than cases. The average initial titers of antistreptolysin of cases, carriers, and non-infected individuals, however, were essentially similar.

Antifibrinolysin

Only 20 per cent of hospitalized cases and only one of 33 carriers exhibited a significant increase in antifibrinolysin titer (table 9). The test was not lacking in specificity since no subject who did not harbor type 5 streptococci had a rise in titer. There is some indication that various types and strains of streptococci vary in their ability to produce fibrinolysin (8). Experiments in this laboratory indicated that the type 5 strains isolated during the epidemic produced a relatively small amount of fibrinolysin. This phenomenon could explain the small number of increases in antifibrinolysin encountered.

Five subjects, 4 of them primary cases and 1 an early secondary carrier, had two-tube rises in titer of antifibrinolysin but not antistreptolysin. On the basis of a response to either antigen, 85 per cent of all hospitalized cases were found to have a significant increase in antibodies.

Serological reactions with pneumococcus C substance

The significance of serological reactions with pneumococcus C substance in acute phase serum is not known. Their occurrence in the sera of patients with pneumococcus pneumonia and a few miscellaneous diseases has been described (9). More than 60 per cent of

hospitalized cases in the present study had such reactions in acute phase sera (table 10). Only one of the carriers showed a reaction with C substance. In the latter, of course, it was not possible to select an "acute phase" serum specimen and the tests were performed on the serum specimens obtained within three days after the subjects were found to harbor type 5 streptococci.

TABLE 9

Antifibrinolysin Response

	NUMBER TESTED	MAXIMUM CHANGE IN TITER IN DILUTION INCREMENTS BETWEEN ACUTE AND CONVALESCENT PHASE SERA					
		0 or decrease		+1		+2 or more	
		No.	Per cent	No.	Per cent	No.	Per cent
Type 5 streptococci not present							
G and Hq. Co.	97	88	91	9	9	0	0
H Co.	117	107	91	10	9	0	0
Total	214	195	91	19	9	0	0
Type 5 streptococci present							
All hospitalized cases	100	54	54	26	26	20	20
All cases	112	64	57	28	25	20	18
Primary	89	50	56	23	26	16	18
Early Secondary	11	6	55	4	36	1	9
Late Secondary	10	6	60	1	10	3	30
All "healthy" carriers	33	29	88	3	9	1	3
Primary	9	8	89	1	11	0	0
Early Secondary	13	13	100	0	0	0	0
Late Secondary	10	8	80	2	20	0	0

Epidemic streptococcal pharyngitis evidently is one of the diseases in which serological reactions with pneumococcus C substance can be found. Previous unpublished observations by this Commission indicated that 80 per cent of patients with sporadic streptococcal pharyngitis or tonsillitis who developed antistreptolysin also showed a reaction with C substance in acute phase sera. Serological reactions with pneumococcus C substance may be detected, apparently, in the majority of cases of streptococcal infection of both sporadic and epidemic varieties.

Other laboratory studies

Sensitivity of type 5 streptococci to sulfadiazine. Buffered dextrose broth, containing sulfadiazine in concentrations varying from 2.5 to 15 mgs. per cent, was inoculated with several strains of type 5 streptococci isolated early in the epidemic. The inocula varied from 100 to 1 million organisms per ml. Visible growth was determined after 18 and 24 hours' incubation. The results indicated a sensitivity to be expected from previous studies (13); small inocula were inhibited

TABLE 10

Serological Reactions with Pneumococcus C Substance in Acute Phase Sera

	NUMBER TESTED	POSITIVE		NEGATIVE	
		No.	Per cent	No.	Per cent
Type 5 streptococci not present					
G. and Hq. Co.	66	1	2	65	98
H Co.	74	0	0	74	100
Total	140	1	1	139	99
Type 5 streptococci present					
All hospitalized cases	91	58	64	33	36
All cases	96	60	63	36	37
Primary	78	50	64	28	36
Secondary	16	10	63	6	37
All "healthy" carriers	11	1	9	10	91

by concentrations of 5 mgs. per cent of drug and large inocula grew despite the presence of 15 mgs. per cent of sulfadiazine. Several strains of Group A streptococci (other than type 5) were found more resistant to sulfonamide.

There was no indication that the strains of type 5 streptococci responsible for the epidemic exhibited any unusual resistance to the action of sulfadiazine. The blood levels obtained from patients during treatment varied from 5 to 15 mgs. per cent of free drug per ml. of blood. The lack of dramatic response to sulfadiazine treatment cannot be ascribed to an unusual degree of resistance of the organisms

to sulfonamides as compared with other Group A strains of β-hemolytic streptococci.

Erythrogenic toxin. Special studies of the ability of the strains to produce erythrogenic toxin were not carried out. However, Dick tests were made on all patients within 24 hours after hospital admission. Commercial erythrogenic toxin (Lederle) was employed and the conventional intradermal method of inoculation used. Erythema measuring 1.0 cm. or more in diameter at the end of 24 hours was considered a positive reaction. Of the 93 patients with type 5 streptococcus infection tested on admission to the hospital, 17 were positive reactors—a rate (18 per cent) which is well within the expected normal range for this age group (2).

Six to seven weeks after the beginning of the epidemic, it was possible to retest 7 of the 17 who were originally positive. All 7 subjects remained Dick positive, despite the fact that they had recovered from streptococcal infection 4 to 5 weeks before. This strain of type 5 streptococcus, therefore, was not a producer of erythrogenic toxin, at least in significant amounts. This was confirmed by the absence of cases of scarlet fever during the outbreak.

Fibrinolysin production by type 5 streptococci. A method was devised to measure the amount of fibrinolysin produced by β-hemolytic streptococci *in vitro* (14). Forty-eight strains of type 5 streptococci isolated from 28 patients either at the time of hospitalization or about six weeks later were tested. All but 2 of the 48 strains produced 80 units of fibrinolysin per ml. of broth. There was no difference in the ability to produce fibrinolysin *in vitro* of streptococci isolated early in the epidemic and six weeks later. Strains recovered after sulfadiazine treatment behaved like those which were not exposed to sulfadiazine.

The ability to produce fibrinolysin *in vitro* varies with different types of Group A streptococci and also with different strains of the same type (8). In this epidemic, however, the uniform ability of all strains tested to produce the same amount of fibrinolysin is further indication of the common source of the infectious agent.

Summary. A rise in titer of antistreptolysin "0" of two or more dilution increments was found during convalescence in 80 per cent of hospitalized patients with type 5 streptococcus infection. A similar rise in titer was found in 31 per cent of "healthy" carriers. Initial

antistreptolysin titers were essentially alike in infected and uninfected subjects. Increases in antistreptolysin titer during convalescence occurred with similar frequency in primary and secondary cases and in primary and secondary carriers.

Twenty hospitalized cases and one carrier had significant rises in titer of antifibrinolysin. Five individuals who did not have two-tube increases in antistreptolysin had two-tube rises in titer of antifibrinolysin. In all, 85 per cent of hospitalized patients had significant increases in titer of either antistreptolysin or antifibrinolysin. Serological reactions with pneumococcus C substance were detected in acute phase sera of 64 per cent of hospitalized subjects. This reaction occurred in the serum of only one carrier.

In vitro studies indicated that strains of type 5 streptococci isolated during the epidemic were not unusually resistant to the bacteriostatic action of sulfadiazine.

The absence of scarlet fever and the Dick reactions during acute and convalescent stages of illness indicated that this strain of type 5 streptococcus did not produce significant amounts of erythrogenic toxin.

All strains tested exhibited uniform ability to produce small amounts of fibrinolysin.

VII. IMMUNOLOGICAL AND CLINICAL CORRELATIONS

Relation of tonsillectomy to the numbers and persistence of streptococci. A clear relationship was found between the presence or absence of tonsils and the numbers of type 5 streptococci recovered from throat cultures taken early in the illness. In table 11, the patients were divided according to whether either or both of the first two throat cultures obtained after admission to the hospital contained β-hemolytic streptococci in predominance, or in numbers amounting to less than 50 per cent of the total colonial growth on blood agar plates. The effects of sulfadiazine can be ignored, since the first culture was taken prior to therapy and the second culture either before or within twelve to twenty-four hours after the beginning of treatment. A predominant growth of streptococci was recovered from more than half of all patients whose tonsils were present, and from less than a quarter of patients who had had tonsillectomy.

The presence of tonsillar tissue may be presumed to offer a favorable site for the nidation and rapid propagation of streptococci. In support of this is the observation previously made that confluent exudate (pseudomembrane) was much more frequent in patients with tonsils than in those with a history of tonsillectomy, even though some of

TABLE 11

Relation of Number of Streptococci in Early Cultures to History of Tonsillectomy

NUMBER OF STREPTOCOCCI	NUMBER WITH TONSILS PRESENT	NUMBER WITH HISTORY OF TONSILLECTOMY
Predominant	33	6
Present	28	21
Total	61	27

TABLE 12

Relation of Tonsillectomy to Persistence of Convalescent Carrier State

	TYPE 5 STREPTOCOCCI AT 6 WEEKS				
	Present		Absent		Total
	No.	Per cent	No.	Per cent	No.
Tonsils present					
No treatment	12	60	8	40	20
Sulfadiazine	21	55	17	45	38
Total	33	57	25	43	58
Tonsillectomy					
No treatment	3	15	17	85	20
Sulfadiazine	2	33	4	67	6
Total	5	19	21	81	26

the latter had a considerable amount of tonsillar tissue in the form of "tags".

Not only was the presence of tonsils associated with a predominance of streptococci early in the illness, but it also appeared to be an important factor in determining the duration of the carrier state during convalescence (table 12). More than half of those patients whose tonsils had not been removed still harbored type 5 streptococci in their

throats six weeks after the beginning of the epidemic, but only one-fifth of those who had tonsillectomy remained carriers of the organisms at this time. These differences were present regardless of the exhibition of sulfadiazine during the illness.

Other investigators (15–17) have pointed out that streptococci persist in the crypts and other relatively inaccessible portions of the tonsillar tissue. One might expect, therefore, that patients with small tonsillar remnants or those with complete tonsillectomy could more easily and quickly rid themselves of the organisms following recovery from streptococcal infection of the upper air passages. This hypothesis is abundantly confirmed in the present study.

Relation of tonsillectomy to initial and convalescent titers of antistreptolysin. The initial and convalescent stage titers (3 and 6 weeks after the beginning of the epidemic) are presented graphically in figs. 16 and 17. Even with the small number of cases significant differences in antistreptolysin titers were seen when patients with a history of tonsillectomy and those with tonsils were compared. The initial titers of the tonsillectomized patients exhibited a wide variation from very low to very high levels. In contrast, those with tonsils—both treated and untreated—showed a narrower range of initial titers. For example, in the tonsillectomized group, more than one-third had initial titers of 100 or less, whereas only one-sixth of those with tonsils had levels of 100 or less. Moreover, high initial titers were also more frequent in the tonsillectomized group than in those whose tonsils had not been removed. Other investigators have noted that tonsillectomized patients have lower titers than those with tonsils at the beginning of an outbreak (18), and have ascribed this difference to the continued stimulus to antibody formation which is presumed to exist in chronic streptococcus carriers with large tonsils (19). This hypothesis seems reasonable but does not explain the variability in initial levels and the tendency for some tonsillectomized patients to have unusually high initial titers. These patients did not give a history of a recent sore throat preceding the present attack. The convalescent titers likewise exhibited wide variation particularly in the tonsillectomized individuals. In this group, titers of 625 units or more were twice as frequent as in those with tonsils.

Effect of sulfadiazine on antistreptolysin response. In figs. 16 and

17, no very obvious differences are revealed in antistreptolysin response between treated and untreated patients. A few more patients in the untreated group exhibited very high titers at 3 and 6 weeks as compared with the sulfadiazine-treated group. In view of the small numbers involved, these differences have no statistical significance.

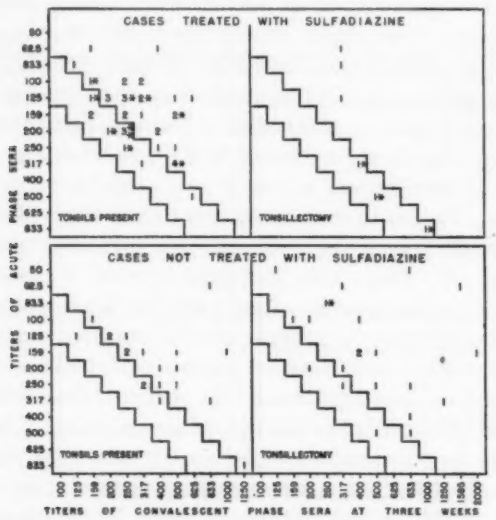


FIG. 16. ANTISTREPTOLYSIN TITERS OF ACUTE PHASE SERA AND CONVALESCENT PHASE SERA 3 WEEKS AFTER THE BEGINNING OF THE EPIDEMIC

Figures refer to number of cases. Areas within diagonal lines represent changes between acute and convalescent titers of less than 2 dilution increments. For meaning of asterisks, see text.

The figures followed by asterisks in figs. 16 and 17 represent cases in which more than half of the daily throat cultures taken while in the hospital yielded no streptococci. Altogether there were 14 such patients in the entire group of 89. Since all but one of these cases were treated with sulfadiazine and since many of them had streptococci in predominance in the initial culture, the disappearance of streptococci during this period was clearly an effect of sulfadiazine. Eight of the 13 cases had less than a two-tube rise in antistreptolysin at 3 weeks, whereas 85 per cent of the sulfadiazine treated cases in which strep-

tococci did not disappear during treatment, had an antistreptolysin rise of two tubes or more (table 13). It appears that sulfadiazine may inhibit the development of antistreptolysin and that this may be effected by a suppression of the antigenic stimulus during the illness. This suppression must have been of considerable magnitude, because more than half of the throat cultures during therapy yielded no streptococci.

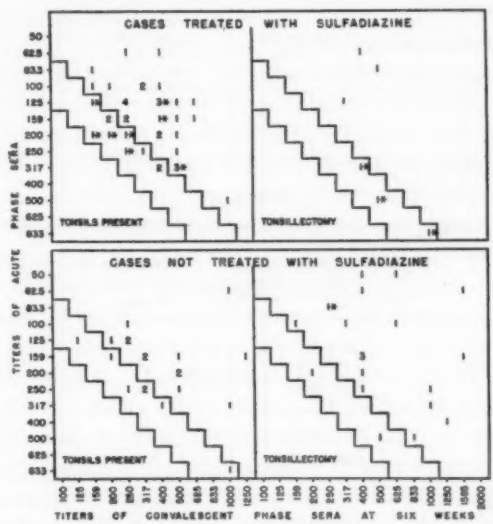


FIG. 17. ANTISTREPTOLYSIN TITERS OF ACUTE PHASE SERA AND CONVALESCENT PHASE SERA 6 WEEKS AFTER THE BEGINNING OF THE EPIDEMIC

For explanation see legend of Figure 16

Relation between height of antibody response and duration of the convalescent carrier state. It has been shown that the duration of the convalescent carrier state is dependent upon the amount of tonsillar tissue present, and specifically upon whether or not tonsillecomy has been performed. This anatomical factor is not the only determining condition on which the carrier state depends. A relationship has also been found between changes in the antistreptolysin level and the carrier state (table 14). Those cases in which type 5 streptococci were still recovered from throat cultures 6 weeks after the

start of the epidemic tended to exhibit smaller increases in titer than those in which the organisms had disappeared. This effect was independent of the effect of tonsillectomy or of sulfadiazine since it

TABLE 13

Relation of Number of Daily Cultures Positive for Type 5 Streptococci During First Week of Hospitalization to Subsequent Antistreptolysin Response in Sulfadiazine Treated Patients

PROPORTION DAILY CULTURES POSITIVE	NUMBER OF CASES	ANTISTREPTOLYSIN TITER CHANGES IN DILUTION INCREMENTS, INITIAL—3 WEEKS		
		0	+1	+2 or more
Less than half	13	3	5	5
Half or more	35	3	2	30

TABLE 14

Relation of Persistence of Convalescent Carrier State to Height of Antistreptolysin Response

	RISE IN ANTISTREPTOLYSIN TITER IN DILUTION INCREMENTS—INITIAL TO 6 WEEKS	TYPE 5 STREPTOCOCCI AT 6 WEEKS	
		Present	Absent
Tonsils			
No treatment	3 or less	9	4
	4 or more	3	4
Sulfadiazine	3 or less	18	8
	4 or more	4	8
Tonsillectomy			
No treatment	3 or less	3	3
	4 or more	0	14
Sulfadiazine	3 or less	0	3
	4 or more	2	1

was demonstrated in all groups except the 6 treated cases who had had tonsillectomy.

A further analysis of this relationship is shown in table 15, in which the disappearance or persistence of type 5 streptococci in throat cultures obtained 3 and 6 weeks after the beginning of the epidemic is compared with changes in the antistreptolysin level during the same interval. The rather surprising result emerges that patients

who continued to harbor the organisms had little further antibody response at 6 weeks, as compared with the levels at 3 weeks, whereas, in those patients whose streptococci disappeared after 3 weeks, the antistreptolysin level continued to rise. This effect, again, appeared to be independent of the effects of either sulfadiazine or tonsillectomy on antibody levels or on the carrier state. Although the number of cases in each group is small, the results have statistical significance.

A definitive explanation for these findings cannot be given. It is reasonable to suppose, however, that the self-sterilization of the mucous membranes of the respiratory passages which marks the termination of the convalescent carrier state may be related to the development of antibacterial antibodies. Antistreptolysin is not such an antibody (11) and the relation between the termination or persistence of the carrier state and the antistreptolysin level is necessarily indirect. The above results, however, lead to the supposition that a relationship existed between the development of antibacterial antibodies and the subsequent height of the antistreptolysin level.

Correlations of clinical severity and immunological status. An attempt was made to relate the severity of the illness to 1) the initial level of antistreptolysin, and 2) the maximum convalescent titer of antistreptolysin. There is no *a priori* reason for believing that the latter relationship exists and we are unaware of any infectious disease in which the severity of the illness can be related to the magnitude of the immunological response. However, the initial immunological status can be related to clinical severity of illness, as recent studies with influenza vaccine have shown (20). Since the results were negative, the tabulations will not be presented. The following indices of severity were tested: severe (3 +) injection of the mucous membranes; maximum amount of pharyngeal or tonsillar exudate; tender and enlarged cervical lymph nodes; maximum temperature of 102° or more; total leucocyte count of 12,000 per cu.mm. or more; positive serological reaction with pneumococcus C substance in acute phase sera; onset of illness before the evening of November 18 (i.e., in a common source epidemic the more severe the illness, the earlier the onset); hospitalization for more than 10 days (development of complications). In each category those cases fulfilling the criteria were compared with the total group with regard to both the initial level

of antistreptolysin and the maximum rise in antistreptolysin during convalescence. The comparisons were made without regard to treatment with sulfadiazine since, in general, patients were most severely ill at the time of admission to the hospital and before the beginning of treatment.

As has been mentioned, it is to be expected that no correlation was found between clinical severity and antibody response. With regard to the lack of correlation between the initial antistreptolysin

TABLE 15

Relation of Change in Titer of Antistreptolysin Between 3 and 6 Weeks and the Persistence of Type 5 Streptococci in the Same Interval

TYPE 5 STREPTOCOCCI		ANTISTREPTOLYSIN—CHANGE IN TITER BETWEEN 3 AND 6 WEEKS									
		Tonsils sulfadiazine		Tonsils no treatment		Tonsillectomy sulfadiazine		Tonsillectomy no treatment		Total	
At 3 weeks	At 6 weeks	0 or less	+1 or more	0 or less	+1 or more	0 or less	+1 or more	0 or less	+1 or more	0 or less	+1 or more
+	0	2	12	2	2	3	1	2	5	9	20
+	+	14	5	9	2	1	1	2	0	26	8

TABLE 16

Relation of the Duration of the "Healthy" Carrier State to Antistreptolysin Response

DAYS BETWEEN FIRST AND LAST CULTURE POSITIVE FOR TYPE 5 STREPTOCOCCI	NUMBER OF SUBJECTS	ANTISTREPTOLYSIN RESPONSE, NUMBER DILUTION INCREMENTS CHANGE—INITIAL TO MAXIMUM TITER		
		0	+1	+2 or more
1– 9	9	9	0	0
10–19	8	1	3	4
20–42	14	4	4	6

level and the clinical severity, it may be pointed out again that this antibody is not antibacterial, but merely reflects previous experience with any streptococcus of Group A. It is possible that the presence of type specific antibodies at the beginning of an illness would modify its subsequent course or prevent it entirely. This procedure had recently been suggested for the prevention and control of streptococcal infections (21).

Duration of "healthy" carrier state in relation to antistreptolysin response. The duration of the "healthy" carrier state was divided

according to the number of days between the first and last culture positive for type 5 streptococci (table 16). Primary and secondary carriers were not separated. A clear-cut distinction appears between those who carried the organisms for less than 9 days (in most instances this represented only one or two cultures positive for type 5 streptococci), and those who carried the organism for a period of 10 days or more. None of the transient carriers developed antibodies while the majority of the others did. Such a sharp distinction in antibody response between the transient carrier state and the carrier state of longer duration suggests again that the definition of a "healthy" carrier is arbitrary. The correlation between the development of antibodies and the persistence of the organisms in the throat indicates strongly that such carriers, in fact, have been parasitized by the organisms and are truly infected. The transient carriers, on the other hand, harbor the organisms in a saprophytic relationship.

Summary. More than half of patients with tonsils had a predominant growth of streptococci in early cultures; while patients who had tonsillectomy only occasionally harbored the organisms in predominance. Those with tonsils frequently remained persistent or chronic convalescent carriers whereas in the majority of individuals who had tonsillectomy the organisms disappeared from the throat within 6 weeks.

Initial levels of antistreptolysin titer tended to be lower in patients with tonsillectomy than in those who had tonsils, but the former group exhibited wider variations in initial titers than the latter. Tonsillectomized patients likewise tended to have higher convalescent titers than patients with tonsils.

An inhibition of the antistreptolysin response was found in those subjects in whom sulfadiazine treatment caused marked suppression of the organisms in the throat.

The antistreptolysin response 6 weeks after the epidemic was smaller in patients who still harbored type 5 streptococci than in those who were no longer convalescent carriers. During the period from 3 to 6 weeks after the epidemic, antistreptolysin titers continued to rise in patients who no longer harbored the organisms but did not continue to rise in those who remained carriers.

No correlation was found between the severity of illness and either

the initial level of antistreptolysin or the magnitude of the antistreptolysin response during convalescence.

Healthy carriers who harbored type 5 streptococci for less than 10 days did not exhibit increases in antistreptolysin titer, whereas half of the healthy carriers who harbored the organisms for more than 10 days did have increases in antistreptolysin titer.

VIII. DISCUSSION

The occurrence of a food-borne epidemic due to type 5 β-hemolytic streptococcus provided an opportunity to investigate the epidemiological behavior of a common source epidemic and to compare the clinical and laboratory findings with those obtained in endemic streptococcal infections.

Epidemiology. The epidemiological features of this outbreak clearly indicated a common source of infection. The onset was explosive, the attack rate was high, and all of the early cases were confined to the men who ate in one mess hall. It is probable that the majority of the men acquired their infection simultaneously, since more than 80 per cent of the primary cases occurred within an interval of 48 hours. Although the exact source of the infection was not established, epidemiological evidence incriminated creamed eggs which were presumably contaminated during the process of preparation. There was a suitable interval for the incubation of a contaminating organism.

Evidence of secondary spread of streptococcal infections following a food-borne epidemic is frequently obscure because of the difficulty of observing an adequate population which is exposed only to secondary infection and not to the primary source. In the present study 133 men in the affected companies were shown by one or more throat cultures to have escaped a primary infection. Of these men, 18 developed subsequent streptococcal illnesses and 22 became carriers. The secondary infections were scattered throughout a six-week period of observation. Although it is possible that these infections were acquired from some intermittent source in the mess hall, it is more probable that they resulted from direct contact with the primary cases, or indirectly from the contaminated environment of the barracks (4). The secondary attack rate for clinical cases was approximately 13 per cent, which is comparable with the rate reported by Stebbins,

Ingraham, and Reed (2) among household contacts in epidemics of contact spread scarlet fever and milk-borne septic sore throat.

Although in the hospital 4 of 19 ward contacts of the epidemic cases, and 1 of 20 attendants, became carriers, in the field the spread of infection beyond the companies originally affected was slight. It is impossible to determine whether or not the limitation of this epidemic was the result of the quarantine procedures, but under the conditions of the epidemic such restrictions appear to have been justified.

The diagnosis of streptococcal infection. Studies on β-hemolytic streptococcal infections of the respiratory tract have been conducted at this laboratory since the autumn of 1942. These studies have dealt chiefly with the clinical and immunological characteristics of endemic (presumably air-borne) infections (22, 23). The incidence of streptococcal disease at this Post has been low and the cases sporadic. Some of the results of the previous studies may be summarized briefly as follows:

The diagnosis of sporadic streptococcal infections of the upper respiratory tract depends on laboratory evidence and, specifically, requires both bacteriological confirmation and the demonstration of an antibody response (antistreptolysin). Accurate diagnosis cannot be made on the appearance of the pharynx alone. While the majority of cases are easily recognized and present the classical or typical features, many patients whose throats do not appear characteristic of streptococcal pharyngitis or tonsillitis actually are found to harbor streptococci and develop antistreptolysin during convalescence. Although exudate is usually present on the tonsils or pharyngeal mucosa, patients may have streptococcal disease without exudate. Conversely, approximately half of all hospitalized patients who had exudate do not harbor streptococci or exhibit an antibody response to the streptococcus. The latter cases usually have smaller amounts of exudate and exhibit a clinical pattern of illness differing from streptococcal infections. These studies have also emphasized that the recovery of β-hemolytic streptococci in throat cultures of patients hospitalized for respiratory disease is not of itself diagnostic. Evidence has been offered that hospitalized patients who harbor streptococci but do not have an antistreptolysin response are merely carriers

of the organisms who concomitantly, suffer from another etiological variety of respiratory disease which leads to hospitalization (23).

The present epidemic allows of certain comparisons of sporadic, air-borne streptococcal infection and epidemic, food-borne infection. The clinical features of the epidemic cases were quite similar, as a group, to the sporadic cases of streptococcal infection described in a previous report (22) and also to earlier descriptions of air-borne streptococcal infections of the throat by other workers (24). An acute onset with feverishness, chilliness and sore throat was characteristic of both sporadic and epidemic cases. The physical appearance of the throat was similar. A short febrile course with rapid subsidence of the initial acute symptoms and slow regression of cervical adenitis and mucosal injection fit the pattern previously described. This similarity suggests that differences in mode of transmission and possible variations in dosage in food-borne as compared with air-borne infections do not seem to play the dominant role in determining the clinical course of the illness. Whether specific types of Group A streptococci vary in the severity of the illness they produce, as they are known to vary in their ability to produce scarlet fever (25), is as yet unknown. A suggestion that this may be so was made in a previous publication on the basis of limited observations (22).

Although the clinical features of most cases in the present epidemic were typical of streptococcal tonsillitis or pharyngitis, some were not and had they been admitted from various organizations and over a longer period of time would not have been recognized clinically as streptococcal infections. For example, only 23 had confluent exudate, while 18 had only pin-point exudate and 6 no exudate at all. Moderate or severe edema of the uvula was found in only 53 per cent of cases. The maximum temperature while in the hospital was less than 100° in 18 per cent of the cases. One patient, admitted from the affected organization during the height of the epidemic, had acute follicular tonsillitis but on 9 daily throat cultures no β-hemolytic streptococci were recovered. One month later he was readmitted, again with an acute onset of fever and sore throat, and with the appearance of the throat similar to the first admission, but on this occasion had type 5 streptococci and subsequently exhibited an antistreptolysin response. Another patient, also a secondary case, had type 5 streptococci in

the throat, but gave a history typical of a febrile "cold"; he did not develop antibodies. Such cases illustrate the variations in clinical pattern and also emphasize that the diagnosis of streptococcal infection depends not only on history and appearance of the throat and on the bacteriological findings but also, and more important, on the demonstration of an antibody response.

During convalescence an increase in antistreptolysin titer of two or more dilution increments (two-tubes) over the initial titer was demonstrated in the sera of 80 per cent of all hospitalized cases with type 5 streptococci recovered from the throat cultures. Four patients who did not have a two-tube rise in antistreptolysin (2 with a one-tube rise and 2 with no rise) had a significant (two-tube) rise to antifibrinolysin during convalescence. Altogether 84 per cent of hospitalized patients had a significant rise in titer of either or both of these antibodies. These findings further confirm the already well established specificity of the antistreptolysin test (26). Recent studies from this laboratory indicate an equal specificity with regard to the quantitative antifibrinolysin test (27).

In addition to the 84 per cent of cases in which a diagnostic antibody response was demonstrated, 12 per cent had a one-tube rise of antistreptolysin during convalescence. In previous reports we have not listed such cases as having a significant increase in titer. This is a conservative attitude and is based on the fact that variations of one-tube may occur as technical errors in the test. Accumulated experience in this laboratory indicates, however, that such differences are usually reproducible, especially at higher titers. It is believed probable that many, possibly the majority, of one-tube rises in titer are significant and indicative of an antistreptolysin response to recent infection. On this assumption, more than 90 per cent of all hospitalized cases of type 5 streptococcus infection had an increase in titer to antistreptolysin or antifibrinolysin during convalescence.

Only 4 hospital patients harboring type 5 streptococci exhibited no increase to either antibody. Two of these patients had a marked suppression of streptococci during the first 10 days of illness as a result of sulfadiazine therapy and their failure to develop antibodies may be accounted for on this basis. In one other patient the history and normal appearance of the throat clearly indicated that he was

suffering from a febrile "cold" and, incidentally, was a carrier of type 5 streptococci. The fourth patient had a history and physical signs in the throat consistent with streptococcal infection, although the exudate was minimal and the temperature did not exceed 99°.

The fact that all but 4 hospitalized cases with type 5 streptococci in the throat developed an increase in titer of either antistreptolysin or antifibrinolysin during convalescence indicates the diagnostic value of antibody determinations. The high percentage of cases exhibiting an antistreptolysin rise is not a peculiarity of the type 5 strains of hemolytic streptococci since all Group A strains (as well as some strains of Groups C and G) also stimulate antistreptolysin (28), and the frequency of the response in other streptococcal infections has been similar to the present experience (26). The antibody studies in this epidemic justify the opinion, previously expressed, that a serological response, rather than the clinical features or the bacteriological findings, should be the determining factor in the diagnosis of streptococcal infections.

Sulfadiazine therapy. The therapeutic value of sulfonamide drugs in the treatment of streptococcal infection of the throat has been supported and denied by numerous conflicting claims (29–34). A comprehensive review will not be attempted. Few reports present data in sufficient detail to offer convincing evidence of the soundness of the conclusions. The negative reports have in general been documented; the affirmative reports have been limited to clinical impressions. In small samples, even strict alternation of cases does not insure comparable groups, as the present study indicates, and bias can rarely be excluded.

From a practical therapeutic standpoint in this study no worthwhile benefit was derived from sulfadiazine. A slight reduction was demonstrated in the frequency of certain consitutional symptoms, such as feverishness, chilliness, and malaise. A more marked reduction in the frequency of sore throat was also effected. Objective evidence of benefit with regard to the local inflammatory reaction in the throat was not found. When due allowance was made for differences in the febrile reaction of patients with and without tonsils, sulfadiazine was found to effect only a slight decrease in the height and duration of fever. In contrast to the meagre effects on symptoms, physical

signs, and fever, sulfadiazine treatment brought about a very considerable reduction in the proportion of elevated total and differential leucocyte counts and in the prevalence of β-hemolytic streptococci in the throat; these effects were transient, however, and persisted only during the time of actual treatment. The therapeutic effect of sulfadiazine became evident only after statistical analysis. The physicians observing the patients during the period of treatment gained the impression that sulfadiazine had no remarkably favorable effects on the course of the disease.

The dosage of drug employed was adequate to secure blood levels in the usual therapeutic range. Since there was evidence that symptoms and certain clinical laboratory findings either persisted or recurred after cessation of treatment, it is possible that a more prolonged course of treatment would have been desirable. However, such prolongation of treatment could not have further modified the course of the initial illness, and could not have reduced the incidence of late non-suppurative complications. Our own previous clinical experience, and that of others (31), indicates that sulfonamide treatment may be of value in aborting or preventing the development of peritonsillar abscess and other septic complications. The present study afforded no opportunity to test this effect.

The effect of sulfonamide therapy on the development of antibodies has been studied to some extent in streptococcal infections. Earlier reports, both clinical (35) and experimental (36), indicated that sulfanilamide did not inhibit an antistreptolysin response to streptococcal infections. The suppression of growth of streptococci effected in these studies was probably incomplete. The present report, as well as the recent work of others (37), indicates that when the suppression of growth of the organisms is more marked, an inhibition of antistreptolysin response may occur. It is not known if antibacterial antibodies are also inhibited, but if such is the case, a suppression of growth of the organisms, short of their complete eradication, would not be a desirable therapeutic goal.

Complications. An unusual opportunity was afforded to study the complications arising from infection of a relatively uniform population by a single type of Group A streptococcus.

Among 100 hospitalized patients, only 2 had frank suppurative

complications. Although several patients had brief recurrences of sore throat, only one was ill enough to require readmission to the hospital. Otitis media and pneumonia did not occur, nor did suppurative lymphadenitis.

The relationship of acute rheumatic fever to streptococcal infection, although still poorly understood, is a well-recognized phenomenon. Many reports, particularly from England, during the past decade, and also from military establishments in this country during the present war, have described epidemics of streptococcal infections, followed, after 2 or 3 weeks, by cases of rheumatic fever (38–44). The reported incidence of rheumatic fever in closed communities, such as schools and barracks, has varied widely depending on the age group involved and other factors. All of these instances of rheumatic fever have been associated with contact (air-borne) epidemics of streptococcal disease. A search of the recent American or English literature failed to disclose any reports of the occurrence of rheumatic fever following food-borne streptococcal infection. In Denmark, however, the subject has been studied and reported quite frequently. Rheumatic fever has followed regularly 2 to 3 weeks after common source food outbreaks of streptococcal infection and with an incidence of approximately 3 per cent (45, 46). These outbreaks were presumably caused by different types of Group A streptococci, since they occurred in different localities and over the course of a number of years, and some were accompanied by scarlet fever, while others were not. Nevertheless the incidence of rheumatic fever was always about the same in each epidemic, which would suggest that various strains and types of Group A streptococci are effective in precipitating rheumatic fever. The hypothesis could be advanced that it is a quality of the susceptible host rather than the invading streptococcus, which selects the victim of rheumatic fever. On the other hand, Kuttner (47) has reached an opposite opinion from her observation that some strains of β-hemolytic streptococci precipitate attacks of rheumatic fever, while others do not. Such divergent observations cannot be harmonized until knowledge of the pathogenesis of rheumatic fever is further advanced.

The occurrence of 3 definite cases of rheumatic fever in the group of 100 cases studied, yields an attack rate of 3 per cent which agrees

closely with the Danish experience cited above. In addition, 2 other patients were suspected as possibly having acute rheumatic fever, but the abnormalities were such that diagnosis could not be established satisfactorily.

Of particular interest, however, was the demonstration in 4 other patients of transient electrocardiographic changes, occurring from 7 to 50 days after the onset of streptococcal infection. The question may be raised legitimately whether T wave changes, such as have been recorded in figs. 11–15 are abnormal and significant of organic disease. A recent series of reports summarizing the electrocardiographic findings in aviation personnel (48–50) showed that inverted or diphasic T waves in leads I or II occurred in only 0.4 per cent of presumably normal young men. The occurrence, therefore, of such T wave changes in four asymptomatic individuals (and a fifth—T317—regarded as a possible case of rheumatic fever), in a group of 100 is far beyond the variations of normal.

It is recognized however that permanent or transient T wave changes may occur in unstable individuals, particularly those with neurocirculatory asthenia (51, 52). Some of the records obtained in this study may well fall in this category, although special studies would be required for proof. The changes in cases T317 (fig. 11) and T265 (fig. 14) may be functional in nature, especially since the T waves are not completely normal in the last records of this series. In cases T207 (fig. 12) and T237 (fig. 13), the character of the changes is probably indicative of structural disease and in case T272 (fig. 15), the combination of both conduction disturbance and T wave changes argues against the functional nature of the changes. One may conclude therefore that abnormalities in the electrocardiogram which were transitory but not necessarily functional, and which may be indicative of pathological alterations in heart muscle, occurred in at least 3 individuals during recovery from streptococcal infection. While these electrocardiographic changes were taking place, these men remained subjectively, and by physical examination, entirely well.

A number of studies have appeared dealing with the electrocardiographic changes during and after streptococcal infection (53–57). Faulkner, Place, and Ohler took serial electrocardiographs during

the course of scarlet fever in children and found approximately 6 per cent who showed electrocardiographic alterations. A much higher incidence of such changes was found by Roelsen in scarlet fever cases, but different criteria of normality make comparisons of one series with another uncertain. Faulkner, Place, and Ohler found the majority of the abnormalities between the 18th and 34th days of illness.

The cause of the electrocardiographic changes found during convalescence from streptococcal infection is not known. Because of the time relationship of these changes to the initial streptococcal infection and because similar electrocardiographic abnormalities occur in known instances of rheumatic fever, it seems reasonable to attribute their pathological basis in some instances to the rheumatic state. Others have reached the same conclusion (53, 56), or have considered the changes non-specific (54, 55).

The ultimate fate of these individuals is not known. In the light of this experience, it becomes easier to realize why so many patients who are seen in later life with rheumatic valvular heart disease give no history of rheumatic fever. Even one of the three frank cases of acute rheumatic fever in this series would probably not have been detected in civilian life since he did not seek medical care but was found to have second-degree heart block and polyarthritis only on a routine follow-up examination. This study most forcefully indicates the necessity and value of routine follow-up examinations in all patients who have had recent streptococcal disease.

Four cases in the series had febrile relapses varying in duration from 6 days to 4 weeks. In none of them was an adequate explanation for the fever found. Such instances of febrile states following streptococcal infections are known to experienced clinicians (58). They have been ascribed, in some instances, to low-grade lymphangitis and lymphadenitis.

There is confusion in the minds of many physicians as to the value of chemotherapy in preventing the complications of streptococcal infections. It is possible that the administration of sulfadiazine early in the course of streptococcal infection may prevent suppurative complications (31). The data of the present study permit no conclusions to be drawn. It may or may not be of significance that

the two patients who had frankly suppurative complications were not treated with sulfadiazine. However, it is clear the sulfadiazine did not prevent the development of late non-suppurative complications, since 8 of the 13 patients who experienced such complications had been treated with sulfonamide. A number of workers have now reported that the prophylactic administration of sulfonamides prevents the development of rheumatic fever by preventing the development of streptococcal infections (59, 60). The present study, however, as well as previous reports (31, 61), emphasizes that once a streptococcal infection has become established, treatment with sulfonamide drugs does not prevent non-suppurative sequelae.

The urinary abnormalities in patients not treated with sulfadiazine are difficult to interpret. Acute glomerulonephritis may be accompanied by minimal urinary findings. Lyttle (62) demonstrated transient hematuria 3 weeks after the onset of scarlet fever in a high proportion of cases. The findings in our study may be similar in nature. However, the occurrence of microscopic hematuria within a week of onset of streptococcal infection is not characteristic of the initial attack of glomerulonephritis. On the other hand, as is illustrated by one case in this study, an exacerbation of chronic nephritis does occur within a few days after the beginning of a streptococcal infection (63).

The urinary findings in the present series of cases can be considered indicative of "focal" nephritis (64). Unfortunately, urine cultures were not made. Moreover, in the absence of bacteremia this diagnosis cannot be substantiated. From the clinical point of view "focal" nephritis is not a well established entity at best, but comes closest to satisfying the observed facts.

IX. GENERAL SUMMARY

A food-borne epidemic of tonsillitis and pharyngitis caused by β-hemolytic streptococci of Group A, type 5, was studied. Epidemiological evidence incriminated creamed eggs served at breakfast as the probable vehicle of infection. The outbreak was explosive in onset, with a median incubation period of 38 hours and a primary attack rate of 42 per cent. Almost all subjects originally infected

became clinically ill. The secondary attack rate was 30 per cent, of which half were cases and half carriers.

The illnesses produced by epidemic type 5 streptococcus infection were mild to moderately severe and did not differ appreciably from sporadic contact, or air-borne, cases of tonsillitis and pharyngitis caused by other types of streptococci at this Post. As in previous studies of sporadic streptococcal infection, the history and appearance of the throat were typical in the majority of cases but in some the diagnosis could not have been made by clinical criteria alone. Pharyngeal or tonsillar exudate was present in 90 per cent of the cases but in only a quarter was it confluent and in another quarter it was no more than pin-head in amount. Although symptoms, physical signs and fever were rapid in onset, maximal in intensity within 48 hours, and declined rapidly, complete return to normal was frequently protracted. Untreated patients who had had tonsillectomy exhibited somewhat more fever than those with tonsils but other significant or consistent differences in clinical severity between the 2 groups were not found.

Alternate patients were treated with sulfadiazine. By statistical analysis slight reduction was demonstrated in the daily frequency of certain symptoms, particularly sore throat, but no objective evidence of benefit was found with regard to the local inflammatory reaction. Only a slight decrease in the height and duration of fever resulted from sulfadiazine treatment. While chemotherapy effected striking reductions in total and differential leucocyte counts and in the daily prevalence of β-hemolytic streptococci in the throat, the changes were transitory and persisted only during the period of treatment. From the standpoint of practical therapeutics no worthwhile benefit was derived from chemotherapy in this epidemic.

Suppurative complications were few but a considerable number of nonsuppurative complications were detected. These included 3 cases of acute rheumatic fever and 2 others in which that diagnosis was suggested but not established. Four other patients had unexplained febrile relapses of 1 to 4 weeks' duration. In addition 4 other subjects who were symptomatically well were found to have transient electrocardiographic changes of uncertain meaning. In some of the individuals these changes were probably not of patholog-

ical significance, but in others the changes may have been indicative of rheumatic myocarditis.

One probable exacerbation of chronic glomerulonephritis was encountered but no examples of acute glomerulonephritis. Transient microscopic hematuria and other urinary abnormalities were detected frequently in the early course of the illnesses. They may have been instances of "focal" nephritis.

A significant rise in titer of antistreptolysin or antifibrinolysin was found during convalescence in 85 per cent of hospitalized cases. Another 12 per cent of cases had a rise in titer of antistreptolysin of less than two tubes. It is probable in many instances that such changes in titer were not due to technical variation; hence an antibody response probably occurred in more than 90 per cent of all cases of type 5 streptococcus infection. Similar antibody responses appeared in nearly half of healthy carriers indicating that a proportion of "healthy" carriers were subclinical cases. Transient carriers did not exhibit an antibody response while those who carried the organisms for more than 10 days did.

The important relationship between the presence or absence of tonsils and streptococcal parasitism was confirmed. Subjects with tonsils frequently had confluent exudate, harbored the organisms in large numbers in early cultures and tended to remain chronic carriers. Subjects whose tonsils had been removed had less exudate, fewer streptococci, and rid themselves of the organisms sooner. Tonsillectomized patients tended to have lower initial levels of antistreptolysin and higher convalescent titers than patients with tonsils.

In those instances in which sulfadiazine suppressed the growth of streptococci to a considerable degree during the first 10 days of illness, an inhibition of antistreptolysin response was demonstrated.

No correlation was found between the severity of illness and either the initial titer of antistreptolysin or the maximum titer during convalescence. However the termination or persistence of the convalescent carrier state did appear to be related to the height of the antistreptolysin response.

ACKLOWLEDGEMENTS

The Commission on Acute Respiratory Diseases wishes to thank the following officers and their staffs at Fort Bragg for assistance in

making this study possible: Major General E. G. Chapman, Commanding General, 13th A/B Division; Lieut. Col. R. F. Bunch, M.C., Surgeon, 13th A/B Division; Major N. S. Irey, M.C., Medical Inspector, 13th A/B Division; Major W. W. Moir, M.C., Surgeon, 513th Parachute Infantry Regiment; Lieut. Col. E. F. Kent, Inf., Commanding Officer, 3rd Battalion, 513th Parachute Infantry Regiment; Major I. A. Edwards, Inf., Executive Officer, 3rd Battalion, 513th Parachute Infantry Regiment; Brig. General H. C. Coburn, Jr., M.C., Surgeon, Fort Bragg; Col. R. C. Tatum, M.C., Assistant Surgeon, Fort Bragg; Col. G. D. Chunn, M.C., Commanding Officer, Regional Hospital; Lieut. Col. W. B. Daniels, Chief of Medical Service; Lieut. Col. H. O. Brown, M.C., Chief of X-Ray Service; Lieut. Col. F. J. Pohle, M.C., Chief of Laboratory Service; and Major S. Solomon, Cardiovascular Diseases Section, Regional Hospital, Fort Bragg.

The Commission on Acute Respiratory Diseases takes pleasure in acknowledging the assistance of the technical staff of the laboratory: Cpl. Alexander Adler, T.Sgt. Louis P. Codifer, S.Sgt. Howard E. Duke, T/5 David O. Foltz, S.Sgt. Eli Gold, Sgt. Curtis Hoover, Sgt. Melvin H. Kaplan, T/5 Gerald J. Leuty, 1st Lt. Walter A. Mickle, Jr., Sn.C., Dorothy Mickle, Sgt. Robert W. Mott, Barbara A. Mulliken, 1st Lt. Thomas J. Oliver, Sn.C., 1st Lt. Ralph Robinson, Sn.C., Irene A. Salamandra, and Sgt. Willard W. Skatrud.

REFERENCES

1. Davis, J. D. Septic sore throat. *The Oxford Medicine*, **V:** 1–9, 1930.
2. Stebbins, E. L., Ingraham, H. S., and Reed, E. A. Milk-borne Streptococcic Infections. Am. J. Pub. Health, **27:** 1259–1266, 1937.
3. Strauss, E., Lowell, F. C., and Finland, M. Observations on the Inhibition of Sulfonamide Action by Para-Aminobenzoic Acid. J. Clin. Invest., **20:** 189–197, 1941.
4. Hamburger, M. Studies on the Transmission of Hemolytic Streptococcus Infections. I. Cross Infections in Army Hospital Wards. J. Infect. Dis., **75:** 58–70, 1944.
5. Hirst, G. K. The Quantitative Determination of Influenza Virus and Antibodies by Means of Red Cell Aglutination. J. Exper. Med., **75:** 49–64, 1942.
6. Swift, H. F., Wilson, A. T., and Lancefield, R. C. Typing Group A Hemolytic Streptococci by M Precipitin Reaction in Capillary Pipettes. J. Exper. Med., **78:** 127–133, 1943.

7. HODGE, B. E., AND SWIFT, H. F. Varying Hemolytic and Constant Combining Capacity of Streptolysins: Influence on Testing for Antistreptolysins. J. Exper. Med., **58:** 277–287, 1933.
8. COMMISSION ON ACUTE RESPIRATORY DISEASES, AND KAPLAN, M. H. A Quantitative Study of the Fibrinolysin-Antifibrinolysin Reaction. Science, **101:** 120–122, 1945.
9. ABERNETHY, T. J., AND FRANCIS, T., JR. Studies on the Somatic C Polysaccharide of Pneumococcus. I. Cutaneous and Serological Reactions in Pneumonia. J. Exper. Med., **65:** 59–73, 1937.
10. FINLAND, M. The Spread of Pneumococcal and Streptococcal Infections in Hospital Wards and in Families. *Aerobiology*, 212–222, A. A. A. S., Washington, D. C., 1942.
11. TODD, E. W. The Effect of Antistreptolysin on Infection of Mice by Haemolytic Streptococci. J. Path. and Bact., **40:** 243–253, 1935.
12. SPINK, W. W., AND KEEFER, C. S. Studies of Hemolytic Streptococcal Infection. II. The Serological Reactions of the Blood During Erysipelas. J. Clin. Invest., **15:** 21–35, 1936.
13. BLISS, E. A., AND DEITZ, H. C. A Comparison of the Bacteriostatic Activities of Some of the Newer Sulfonamide Compounds. Bull. Johns Hopkins Hosp., **75:** 1–13, 1944.
14. COMMISSION ON ACUTE RESPIRATORY DISEASES. To be published.
15. BLOOMFIELD, A. L., AND FELTY, A. R. Definition of Hemolytic Streptococcus Parasitism in the Upper Air Passages of Healthy People. Arch. Int. Med., **32:** 386–400, 1923.
16. BLOOMFIELD, A. L., AND FELTY, A. R. Bacteriological Observations on Acute Tonsillitis with Reference to Epidemiology and Susceptibility. Arch. Int. Med., **32:** 483–496, 1923.
17. WHEELER, S. M., AND JONES, T. D. Factors in the Control of the Spread of Acute Respiratory Infections with Reference to Streptococcal Illness and Acute Rheumatic Fever. Am. J. Med. Sci., **209: 58–64, 1945.**
18. RANTZ, L. A. Group A Hemolytic Streptococcus Antibodies. III. A Study of the Simultaneous Infection of a Large Number of Men by a Single Type. Arch. Int. Med., **73:** 238–240, 1944.
19. RANTZ, L. A., JACOBS, A. H., AND KIRBY, W. M. M. Group A Hemolytic Streptococcus Antibodies. II. Griffith Type Agglutinin and Antistreptolysin Titers in Carriers and Non-Carriers. J. Clin. Invest., **22:** 419–423, 1943.
20. HIRST, G. K., RICKARD, E. R., AND FRIEDEWALD, W. F. Studies in Human Immunization Against Influenza. Duration of Immunity Induced by Inactive Virus. J. Exper. Med., **80:** 265–273, 1944.
21. SCHWENTKER, F. F., HODES, H. L., KINGSLAND, L. C., CHENOWOTH, B. M., PECK, J. L. Streptococcal Infections in a Naval Training Station. Am. J. Pub. Health, **33:** 1455–1460, 1943.

22. Commission on Acute Respiratory Diseases. Endemic Exudative Pharyngitis and Tonsillitis. Etiology and Clinical Characteristics. J. A .M. A., **125:** 1163–1169, 1944.

23. Commission on Acute Respiratory Diseases. The Rôle of β-Hemolytic Streptococci in Common Respiratory Diseases. Am. J. Pub. Health, **35:** 675–682, 1945.

24. Felty, A. R., and Hodges, A. B. A Clinical Study of Acute Streptococcus Infection of the Pharyngeal Lymphoid Tissue (Acute Follicular Tonsillitis). Bull. Johns Hopkins Hosp., **34:** 330–335, 1923.

25. Hamburger, M., Hilles, C. H., Hamburger, V. G., Johnson, M. A., and Wallin, J. G. Ability of Different Types of Hemolytic Streptococci to Produce Scarlet Fever. J. A. M. A., **124:** 564–566, 1944.

26. Mote, J. R., and Jones, T. D. Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis. J. Immunol., **41:** 35–118, 1941.

27. Commission on Acute Respiratory Diseases, and Kaplan, M. H. Studies of Streptococcal Fibrinolysin. IV. Clinical Application of Antifibrinolysin Test. To be published.

28. Todd, E. W. The Streptolysins of Various Groups and Types of Haemolytic Streptococci; A Serological Investigation. J. Hyg., **39:** 1–11, 1939.

29. Freis, E. D. The Treatment of Tonsillitis with Small Doses of Sulfonamides. J. A. M. A., **126:** 93–94, 1944.

30. Gettelman, E., and Kaiz, S. P. The Treatment of Severe Tonsillitis in a Naval Dispensary. U. S. Naval Med. Bull., **42:** 399–402, 1944.

31. Neukirch, F., Zable, V., Baumgarten, I. A Comparative Study of the Occurrence of Complications in Scarlet Fever Treated with Sulfanilamide, Specific Immune Serum and Normal Horse Serum, with a Reference to Certain Clinical Features of the Material. Acta. Med. Scandinav., **113:** 11–41, 1943.

32. Top, F. H., and Young, D. C. The Treatment of Moderately Severe Scarlet Fever. A Study of Alternate Patients Treated with Sulfanilamide, Convalescent Serum and Scarlet Fever Antitoxin. J. A. M. A., **117:** 2056–2060, 1941.

33. Rhoads, P. S., and Afremow, M. L. Sulfanilamide in Treatment of Sore Throat due to Hemolytic Streptococci, with Controls. J. A. M. A., **114:** 942–943, 1940.

34. French, J. O. The Sulphanilamide Treatment of Scarlet Fever. J. Hyg., **39:** 581–596, 1939.

35. Lockwood, J. S., Coburn, A. F., and Stokinger, H. E. Studies on the Mechanism of the Action of Sulfanilamide. I. The Bearing of the Character of the Lesion on the Effectiveness of the Drug. J. A. M. A., **111:** 2259–2264, 1938.

36. Green, C. A. The Effect of Prontosil Therapy on the Antistreptolysin O Titre in Rabbits During Immunization. J. Path. and Bact., **53:** 213–221, 1941.

37. RANTZ, L. A., KIRBY, W. M. M., AND JACOBS, A. H. Group A Hemolytic Streptococcus Antibodies. I. Griffith Type Agglutinin and Antistreptolysin Titers in Normal Men and in Acute Infections. J. Clin. Invest., **22:** 411–417, 1943.

38. GLOVER, J. A., AND GRIFFITH, F. Acute Tonsillitis and Some of its Sequels: Epidemiological and Bacteriological Observations. Brit. Med. J., **2:** 521–527, 1931.

39. BRADLEY, W. H. Epidemic Acute Rheumatism in a Public School. Quarterly J. Med., **1:** 79–98, 1932.

40. THOMSON, S., AND GLAZEBROOK, A. J. Infectious Diseases in a Semi-Closed Community. J. Hyg., **41:** 570–615, 1941.

41. GREEN, C. A. Epidemiology of Haemolytic Streptococcal Infection in Relation to Acute Rheumatism. I and II. J. Hyg., **42:** 365–370, 371–379, 1942.

42. DITKOWSKY, S. P., STEVENSON, E., AND CAMPBELL, J. M. An Epidemic of Rheumatic Fever in a Children's Institution. J. A. M. A., **121:** 991–995, 1943.

43. HOLBROOK, W. P. The Army Air Forces Rheumatic Fever Control Program. J. A. M. A., **126:** 84–87, 1944.

44. COBURN, A. F. The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy. J. A. M. A., **126:** 88–93, 1944.

45. MADSEN, TH., AND KALKAK, K. Investigations on Rheumatic Fever Subsequent to Some Epidemics of Septic Sore Throat (Especially Milk Epidemics). Acta. Path. et Microbiol. Scandinav., **17:** 305–327, 1940.

46. HENNINGSEN, E. J., AND ERNST, J. Milk Epidemic of Angina, Originating from a Cow with Mastitis and due to Streptococcus Pyogenes (Lancefield Group A). J. Hyg., **38:** 384–391, 1938.

47. KUTTNER, A. G., AND KRUMWIEDE, E. Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three-Year Study. J. Clin. Invest., **20:** 273–287, 1941.

48. HALL, G. E., STEWART, C. B., AND MANNING, G. W. The Electrocardiographic Records of 2000 R. C. A. F. Aircrew. Canadian Med. Assn. J., **46:** 226, 1940.

49. STEWART, C. B., AND MANNING, G. W. A Detailed Analysis of the Electrocardiograms of 500 R. C. A. F. Aircrew. Am. Heart J., **27:** 502–523, 1944.

50. GRAYBIEL, A., MCFARLAND, R. A., GATES, D. C., AND WEBSTER, F. A. Analysis of the Electrocardiograms Obtained from 1000 Young Healthy Aviators. Am. Heart J., **27:** 524–549, 1944.

51. GRAYBIEL, A., AND WHITE, P. D. Inversion of the T-Wave in Lead I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia. Am. Heart J., **10:** 345–354, 1935.

52. WENDKOS, M. H. The Influence of Autonomic Imbalance on the Human Electrocardiogram. I. Unstable T Waves in Precordial Leads from Emotionally Unstable Persons without Organic Heart Disease. Am. Heart J., **28:** 549–567, 1944.
53. ROELSEN, E. Electrocardiographic Studies in Scarlet Fever. Acta. Med. Scandinav., **106:** 26–56, 1941.
54. WESSELHOEFT, C. Medical Progress: Cardiovascular Disorders in Scarlet Fever. New Eng. J. Med., **224:** 942–947, 1941.
55. HOTZ, H. W., AND HUBER, W. Elektrokardiographische Veranderung im Verlaufe akuter Tonsillenerkrankungen. Cardiologia, **4:** 40–74, 1940.
56. FAULKNER, J. M., PLACE, E. H., AND OHLER, W. R. The Effects of Scarlet Fever Upon the Heart. Am. J. Med. Sci., **189:** 352–358, 1935.
57. SHOOKHOFF, C., AND TARAN, L. M. Electrocardiographic Studies in Infectious Diseases. Am. Heart J., **6:** 541–547, 1931.
58. KEEFER, C. S. The Late Non-Suppurative Disorders of Hemolytic Streptococcal Diseases. Texas State J. Med., **35:** 457–468, 1939.
59. COBURN, A. F., AND MOORE, L. V. The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, with Especial Reference to Rheumatic Fever. J. Clin. Invest., **18:** 147–155, 1939.
60. COBURN, A. F. The Control of Streptococcus Hemolyticus. Military Surgeon, **96:** 17–40, 1945.
61. GLAZEBROOK, A. J., AND THOMSON, S. Sulfonamide Compounds and Acute Rheumatism. J. Hyg., **42:** 20–22, 1942.
62. LYTTLE, J. D. Addis Sediment Counts in Scarlet Fever. J. Clin. Invest., **12:** 95–103, 1933.
63. SEEGAL, D., AND EARLE, D. P. A Consideration of Certain Biological Differences Between Glomerulonephritis and Rheumatic Fever. Am. J. Med. Sci., **201:** 528–539, 1941.
64. FORBUS, W. D. *Reaction to Injury.* Williams and Wilkins, Baltimore, 1943.

SUPPRESSION AS AN ADJUNCT TO THE THERAPY OF MALARIA IN NON-MALARIAL AREAS

ROGER A. LEWIS, Captain AND FRANK W. KIBBE, 1st Lieutenant,
Medical Corps, Army of the United States

For two years it has been possible to follow the course of malaria in troops infected with *Plasmodium vivax*. The tendency for this variety of vivax malaria to relapse is well known, although the brief interval between successive attacks is less well appreciated.

The observations reported here were made in an area free of anopheline mosquitoes where there was no possibility of reinfection. Experience with an entire division ever a ten month period led to the developments in therapy that are here reported.

All the individuals in this study were members of the Medical Detachment of a General Hospital. It was possible to secure complete follow-up studies with these men. The cooperation of the men and of the members of the Hospital staff is gratefully acknowledged.

This report presents a method for the treatment of relapsing malarial fever caused by *Plasmodium vivax* of a variety causing frequent early relapses and is not intended to apply to malaria caused by all varieties of parasite.

THE PROBLEM

Mass treatment and energetic therapy for individual attacks will not prevent early (three to six weeks) relapse in the majority of cases. The end result of such relapses is a clinical picture characterized by symptoms of asthenia and in some instances by debility and weight loss. Attempts to lengthen the period between relapses by increasing the dose of atabrine or by prolonging the period of conventional dosage have been unsuccessful and moreover sometimes resulted in minor toxic disturbances.

Because of the incapacitating effect of recurrent malaria, many individuals and some units have been placed on suppressive doses of atabrine once exposed to the disease, even when subsequently stationed in non-malarial areas.

There are however certain drawbacks to the long continued use of suppressive doses of atabrine when military considerations do not require it. There is no evidence in the case of infection with *Plasmodium vivax* that continued suppression will do more than delay the long and costly period of "demalarialization". Furthermore there are obvious objections to continuing any medication beyond the necessary period.

These considerations apply particularly to individuals in units where the majority of personnel has not been exposed to malaria such as the group herein described. They also apply to persons who are no longer on active duty in the armed forces.

PLAN OF TREATMENT

More than two decades ago a national malaria committee in the United States recommended the administration of a two months course of small doses of quinine following the initial dose needed for the control of malarial symptoms (1). Later reports from the League of Nations criticized this schedule and advocated that treatment be limited to one week, partly because of the hypothesis that frequent relapses promote the development of immunity (2). Atabrine in suppressive doses as an adjunct to the conventional course of treatment has been used (3) but has not been generally advocated.

Although the administration of atabrine in suppressive doses will not prevent eventual relapses, it should insure that these are spaced over a longer interval. If relapses are sufficiently delayed the patient has a better chance of recovering from the debilitating effects of each attack. The length of time during which suppression is given may be varied to suit the individual case. In general two months of treatment with 0.1 gram of atabrine daily following the routine seven day course (4), is the method of choice.

Early in November 1943 this plan of treatment was applied to a few individuals in the Medical Detachment of a General Hospital. Late in January 1944 this regime was officially recommended by the Chief of the Medical Service and applied to patients from other units.

RESULTS

Although some of the men were started on suppression in November and December 1943 following the routine clinical treatment of malarial attacks, this was not a general policy until January 1944. The majority of men with malarial attacks in October and November of 1943 was not given suppression following clinical treatment, and serves as a valuable control group.

Before the institution of suppressive treatment the malaria rate among the 63 men of the Detachment who had been exposed to the disease was approximately 4,000 attacks per 1,000 men per annum. During the three months prior to the use of suppression as an adjunct to treatment there were 62 malarial relapses among the group. Some

TABLE I

Number of Individuals That Have Received Two Months of Suppressive Medication and Number of Attacks of Malaria in the Entire Group

	SEPT.	OCT.	NOV.	DEC.	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY
Not suppressed....	63	63	56	48	45	34	32	31	30	30	30
Over suppression...	0	0	0	1	6	9	17	23	27	26	28
On suppression....	0	0	7	14	12	20	14	9	6	7	5
Malarial attacks...	18	20	24	8	13	3	4	6	3	5	2

of the men did not have any attacks after leaving the malarial area so that the rest of the men bore the brunt of attacks. During the three months mentioned above seven men had three attacks, twelve had two attacks and seventeen had one attack.

During the months of December and January, following the institution of two months of suppressive medication after treatment of relapses, the malaria rate was somewhat reduced. From February to August of 1944 the malaria rate fell to approximately 750 attacks per 1,000 men per annum. At no time was it necessary to suppress more than a third of the group and by April there were only nine men remaining on suppression, Table I. Regardless of the relapse percentage it may be seen that the malaria rate was greatly reduced as a result of the long interval between relapses.

All seven men who received suppressive treatment commencing in

November have been followed for nine months. One relapsed in the second month after stopping suppression, two cases relapsed in the fifth month and two during the sixth month while two cases did not relapse.

During the month of December eight more cases were started on suppression following clinical treatment for attacks the previous month. One case relapsed during the third month, one during the fourth month and one during the eighth month while five cases did not relapse during the eight months of observation, having been off atabrine suppression for six months.

During the month of January five more men were started on suppression. Of these men, one relapsed during the third month and one during the sixth month while the remaining three cases did not relapse during the seven months of observation of which five were without atabrine.

In February ten more cases were started on suppression following clinical treatment for attacks the previous month. Three relapsed during the third month, two during the fourth month and two during the fifth month while the other three had no relapses during the six months of follow up.

Of the thirty-five individuals who had relapses during these four months, but who were not given suppressive medication following treatment of the attack, seventeen relapsed during the first month and eleven during the second month while seven did not relapse during the period of observation. The clinical treatment most frequently employed was 2.8 grams of atabrine during a seven day period (4).

In Table II the first thirty cases that received suppression after treatment are compared with the thirty-five cases occurring during the same time but which were not given suppression after clinical treatment. In the unsuppressed group there were twenty-eight relapses from thirty-five attacks occurring at an average time of less than six weeks from the previous attack. In the suppressed group there were seventeen relapses from thirty attacks occurring at an average time of over four months from the previous attack.

The relapse rate with conventional treatment was therefore eighty per cent compared with approximately sixty per cent in the group that was given two months of suppression. However it is probable

that the relapse rate in the latter group will rise after a longer interval. Even if the relapse percentage rose to a figure near that of the unsuppressed cases there would still be a marked lowering of the malaria rate because of the prolonged interval between relapses.

Many of the men who received suppression gained weight. This was especially true when repeated attacks of malaria had been associated with weight loss. In most instances headaches and weakness

TABLE II

Recurrence and Interval between Attacks in Cases not Given Suppression

DATE OF ATTACK	NUMBER OF CASES	NUMBER OF MONTHS BEFORE RELAPSE									TOTAL RELAPSES
		One	Two	Three	Four	Five	Six	Seven	Eight	Nine	
Oct.	14	9	2	0	0	0	0	0	0	0	11
Nov.	15	4	7	0	0	0	0	0	0		11
Dec.	3	3	0	0	0	0	0	0			3
Jan.	3	1	2	0	0	0	0				3
Total	35	17	11	0	0	0	0				28

Recurrence and Interval between Attacks in Cases Given Two Months Suppression

DATE OF ATTACK	NUMBER OF CASES	NUMBER OF MONTHS BEFORE RELAPSE									TOTAL RELAPSES
		One	Two	Three	Four	Five	Six	Seven	Eight	Nine	
Oct.	7	0	1	0	0	2	2	0	0	0	5
Nov.	8	0	0	1	1	0	0	0	1		3
Dec.	5	0	0	1	0	0	1	0			2
Jan.	10	0	0	3	2	2	0				7
Total	30	0	1	5	3	4	3				17

cleared up although this was not invariably the case. In general there was a marked improvement in morale associated with infrequent periods of hospitalization. This was particularly significant since all the men in the series had been transferred into the Medical Detachment because of recurrent malaria or some other disability which interfered with combat duty.

DISCUSSION

The use of suppressive doses of atabrine in non-malarial areas has been criticized for several reasons. Some of the objections to this

form of treatment may be dismissed, some must be weighed against the benefits that are derived, and still others should be the subject of long range study.

Just as some soldiers avoid taking atabrine for fear that it may lead to some personal injury, so persons discourage the use of atabrine in non-malarial areas on the grounds that it may be toxic. However no toxic reactions have been reported in suppressive medication following clinical treatment.

Another objection to the use of suppression in small portions of a military unit is that it entails added administrative work to enforce discipline. However, it is felt that the benefit derived from suppresion justifies this effort.

It has been suggested that suppressed malaria may be just as harmful as repeated clinical attacks. However in this series of cases, in no instance was the period of suppression marked by an aggravation of symptoms, while in many cases there were objective and subjective indications of improvement during the period of suppression.

The theoretical objection that if each attack of malaria is followed by suppressive treatment for two months there may be a delay in the eventual "cure" of the disease has been brought forward. This study and other observations suggest that this is probably not true. A slight reduction in the recurrence percentage will more than make up for the increased interval between attacks in the time required for "cure". However this point cannot be settled without further study.

It is recognized that this series of cases is limited in number and length of follow-up period. Nevertheless it seems advisable to report the results so that a further trial of this plan may be given. Furthermore it is felt that sufficient benefit is derived by some patients from the limited use of suppression immediately following treatment to make the results known.

SUMMARY

The use of drug suppression as an adjunct to therapy in the treatment of malarial relapses is described. According to the plan, the clinical treatment of each recurrence is followed by two months of suppressive atabrine, when there is a tendency for early relapse.

This type of treatment has been gradually introduced into a group of sixty-three individuals who were exposed to malaria. The treatment has been found to increase the interval between relapses from less than six weeks to more than four months. There is consequently a reduction in the malaria rate and in the relative number of man days lost through hospitalization. Furthermore there is an apparent lowering of the relapse percentage, in this series from eighty to less than sixty per cent. The treatment is helpful in increasing the efficiency and morale of affected personnel.

Although continuous suppression may be the method of choice for troops that are highly "malarialized" and needed for active duty or expected to return to a malarial area, the use of two months suppression as an adjunct to the clinical treatment of relapses is of value in other instances. This is especially true in units where the majority of persons have not been exposed to malaria and for individuals who are not expected to return to active duty.

BIBLIOGRAPHY

1. The Treatment of Malaria. Report of the National Malaria Committee. United States Public Health Reports, **34:** 2959, 1919.
2. The Treatment of Malaria. Fourth General Report of the Malaria Commission. Bull. Health Organization, League of Nations, **6:** 895, 1937.
3. The Diagnosis and Treatment of Malaria in England. Warrington Yorke. British Medical Journal, **4254:** 61, 1942.
4. The Drug Treatment of Malaria, Suppressive and Clinical.[1] Circular Letter Number 153. Office of the Surgeon General, Washington, D. C. August 19, 1943.

---

[1] Superseded since preparation of this manuscript by: TB Med, 72, July 10, 1944.

A STUDY OF SPASTICITY AND PARALYSIS

PHILIP F. WAGLEY

Department of Anatomy, Johns Hopkins University

INTRODUCTION

There are two elements in paralysis of cortical origin; (1) loss of control of certain movements and (2) alteration in muscle tone. In cases of hemiplegia, these two qualities are present in various degrees. When the site of the lesion is capsular or cortical, histological sections of the spinal cord, if they reveal damage, show changes in the area commonly assigned to the lateral corticospinal (pyramidal) tract. The residual alteration in muscle tone in such cases is usually hypertonic and is frequently associated with phenomena that are characteristic of spasticity.[1] It was concluded, therefore, that these physiological facets resulted from the corticospinal tract damage. Although more critical analysis of clinical, pathological, and experimental studies has revealed the error in this concept, the location of the spinal cord fibers, the interruption of which results in spasticity, has not been ascertained. It is the purpose of this study to demonstrate that spasticity and paralysis are two physiological states having separable anatomical bases in the spinal cord. In so doing consideration has been given in detail of the effects of pyramidal and various spinal cord lesions on skeletal muscle. Certain physiological results have been ascribed to damage to particular fiber groups. And the effects of the lesions made in this experiment have been compared with the sequelae of other central nervous system lesions.

[1] The term spasticity used here refers to the symptoms grouped by Hughlings Jackson (1) as phenomena of release. In spastic hemiplegia following capsular and cortical lesions in man these signs are hypertonus, clonus, brisk tendon reflexes (some of which recruit more proximal muscles), associated movements, and the positive Babinski. The hypertonus, judged by increase in resistance to passive movement, is claspknife in quality. This group of symptoms were listed as spastic by the older savants of clinical Neurology (2, 3, 4). To this group Walshe (5) added exaggeration of reflexes of muscular and labyrinthine origin. With the exception of the Babinski these can be considered the signs of spasticity in Macaca mulatta.

Materials and Methods

Seven monkeys (Macaca mulatta) ranging from two to four years of age were used. A careful neurological examination was done prior to operation to rule out possible abnormalities. Ether anesthesia was used. The operative approach was through the sixth to eighth thoracic vertebral lamina. This level was chosen for three reasons; (1) trauma to existing nerves would not confuse the findings in the affected appendage, (2) removal of lamina at this location gives more adequate exposure of the lateral aspect of the cord than removal of any lamina caudally, and (3) the transverse processes with the associated intrinsic dorsal musculature are less of an obstacle at this level. After adequate exposure of the dura (4 to 6 mm.) it was slit longitudinally. A cystatome knife was used for the incision in the spinal cord. It was slipped between the dura and pia-arachnoid, the cutting edge turned parallel with the cord. After reaching the most ventral point desired, the instrument was turned at a right angle and the cord partially sectioned. Monkeys W5, W8 and W9 underwent one such operation. W1 and W3 were operated upon twice; W1 once on each side and W3 twice on the same side. The results will be referred to as W1L and W3L (meaning left leg affected by the first operation), W1R (right leg affected by the second operation), and W3L2 (signifying that the second operation on the same side superimposed its effect upon that of the first). This is permissible as each cord lesion affected only the ipsilateral leg and foot. Two animals (W7P and 510P) had unilateral pyramidal sections.[2] In both cords a lesion was made subsequently on the side opposite the pyramidal section in order to superimpose the results of the second operation on the already affected leg. These preparations are designated W7PC and 510PC. The animals were kept alive from 21 to 960 days. They were examined repeatedly. The normal lower extremities are not discussed except for comparison with those on the side of the lesion. The operative site, and blocks from the cervical, thoracic, lumbar, and sacral levels were cut serially and stained by the Marchi, Weigert, Bodian, Quigley-Smith modification of Weigert, Bielschowski, and Spielmeyer tech-

[2] The author wishes to thank Dr. Sarah S. Tower for making these pyramidal preparations.

niques. Sections of the medulla and midbrain of three animals (W1, W5 and 510) were stained by the Nissl method. By killing some of the animals three weeks after a second operation and staining the sections, byWeigert and Marchi techniques, the fibers cut at the first and second operations were differentiated.

Anatomical Results

1) *Lateral Funiculus Lesions:* Lesions of various degrees were made in the lateral aspect of the cord in four animals (W8R, W9L, W5L, W3L). (See diagrams). In one of them (W3L) only the pyramidal and dorsal spinocerebellar tracts were interrupted. The damage to the pyramidal tract, however, was very extensive in this animal in contrast to its partial injury in the others. In W8R and W9L small portions of the pyramidal (more in W8R than W9L), rubrospinal, and lateral reticulospinal tracts were involved, associated with degeneration in the dorsal spinocerebellar tract of W9L and in the dorsal and ventral spinocerebellar tracts of W8R. The other animal in this group (W5L) showed a more localized damage in the most lateral aspect of the cord resulting in extensive degeneration of the lateral reticulospinal and rubrospinal tracts, of a small portion of the dorsal and ventral spinocerebellar, and possibly lateral spinothalamic tracts, and with slight encroachment on the area of the pyramidal fibers. Midbrain sections of W5L showed retrograde degeneration in the right red nucleus and in the reticular formation on the right.

2) *Ventral Funiculus Lesion:* In W1L only some fibers of the ventral funiculus were cut. These severed tracts included the vestibulospinal, ventral spinothalamic, and ventral reticulospinal. (See following section for remarks on midbrain.)

3) *Combined Lateral and Ventral Funiculus Lesions:* In W1R a section of the lateral and ventral quadrants was made cutting the areas of the dorsal and ventral spinocerebellar, lateral and ventral spinothalamic, vestibulospinal, rubrospinal, part of the lateral corticospinal tracts and possibly lateral reticulospinal fibers. The damage to the latter area was so slight it is not demonstrated in the diagram. Midbrain sections of this animal (W1) showed chromatolysis in the left red nucleus (W1R) and chromatolysis, shrinkage of cells, and fibrosis in the reticular formation on both sides (W1L, W1R (?)). In W3L2 the incision was much deeper so that in addition to the fibers enu-

merated above, more of the pyramidal and ventral spinothalamic fibers, as well as the lateral and ventral reticulospinal, rubrospinal, and ventral corticospinal[3] tracts were cut.

4) *Pyramidal and Combined Pyramidal-Spinal Cord Lesions:* Two animals (W7P and 510P), had unilateral pyramidal sections of the medullary pyramids. Subsequently an incision in the lateral and ventral aspects of the spinal cord was also made in one of them (W7PC), thus severing the dorsal and ventral spinocerebellar, lateral spinothalamic, lateral reticulospinal, rubrospinal, and vestibulospinal tracts. In the other monkey (510P) a second operation severed nerve fibers in the lateral funiculus. This preparation (510PC) showed degeneration not only of the pyramidal tract but also of the dorsal spinocerebellar, lateral reticulospinal, and rubrospinal tracts. The midbrain sections of the 510 preparation showed chromatolysis in the right red nucleus and in the reticular formation on both sides.

Physiological Results

1) Alteration of postural activity and impairment of movement

Alterations in the postural use and the movement of muscles were studied by the following nine methods.

(1) Dropping Reactions. When a blindfolded normal animal is dropped the labyrinthine stimulation causes protraction and slight abduction of the hip, extension of the knee, and ventriflexion of the ankle with abduction and extension of the toes.

(2) Lifting Rreactions. When an animal is lifted by the observer the animal's foot normally maintains contact as long as possible with the supporting surface. This "magnet reaction" is a response to cutaneous exteroceptive stimulation (8) and has an extension and a flexion phase. The first phase tends to maintain the contact. When that effort fails it is replaced by the flexion phase in which protraction at the hip, flexion of the knee, and dorsiflexion of the ankle occurs.

(3) Positive Supporting Reaction. Normally, pressure on the foot

[3] Mettler (6) states "the monkey is devoid of a ventral corticospinal tract". Nevertheless, sections of the spinal cord of the Macaca mulatta prepared by the Marchi technique subsequent to a lesion of one pyramid (7) show blackened myelin fragments in the ventral funiculus of the spinal cord, denser in the cervical and upper thoracic levels than in the lumbar and sacral divisions.

pads causes the leg to assume a pillarlike rigidity. The afferents mainly concerned are the tactile receptors of the skin and the proprioceptive endings in the ventriflexors of the foot and ankle.

(4) Placing Reactions. These were tested according to the procedures outlined by Bard (9).

(5) Stepping Reactions. The coordinated movements of stepping were tested by holding the animal so that it stood on both legs. The animal was then moved forward, backward, and to either side. Normally the positive supporting reactions in both legs are strong but with displacement of the body the supporting tone diminishes in one leg, the foot is raised and moved in the direction of diplacement and put down again to support the body in its new position. This is repeated alternately with each appendage as long as passive movement of the body continues.

(6) Hopping Reactions. The coordinated movements of an extremity required for hopping were tested by holding the animal so that it stood on one leg. The body was then displaced in various horizontal directions above a supporting surface. Normally as the body is translated in one direction the appendage used tends to step beneath the center of weight. When moved forward this is done by an initial protraction of the extremity; backward by retraction; lateralward by abduction; and medialward by adduction. Usually the contact is made on the distal pads with adduction of the phalanges, extension of the metatarsophalangeal joints, and slight flexion of the phalangeal joints.

(7) Voluntary Movements. Alterations in the manner of moving about the cage after operation were recorded.

(8) Associated Movements. Normally accompanying the use of an appendage the opposite one may move in a rather purposeless manner. The degree of such involuntary movement was noted in the various animals before and after operation.

(9) Atrophy. The circumferences of the normal and affected appendages of some of the animals were measured at similar levels and the results compared. Such measurements showed not only wasting of the affected leg but in some instances (W1L and W5L) unequal development of the legs. For the sake of simplicity any difference in leg circumference was called an indication of "atrophy" in the smaller leg.

a) *Dropping and Lifting Reactions*

The following observations show that all the pyramidal and spinal cord lesions altered the response to the stimuli of dropping and lifting. A small, isolated lesion in the ventral funiculus had only a slight effect.

(1) *Lateral Funiculus Lesions:* W5L, while held in the air before dropping, kept the affected leg protracted at the hip, flexed at the knee and ventriflexed at the ankle. The opposite or normal leg was in retraction at the hip, with extension greater than flexion at the knee, and dorsiflexion greater than ventriflexion at the ankle. In descending through the air the affected leg remained as it was until the normal one touched the floor. On contact the normal leg protracted, than retracted at the hip, flexed, then extended at the knee; dorsiflexed than ventriflexed at the ankle. There was no jarring and the alternate movements were smooth and graceful. The abnormal leg on contact protracted less at the hip, flexed less at the knee, and remained ventriflexed at the ankle. The subsequent reversal of these movements did not occur as gracefully and quickly as normally. The ankle remained in ventriflexion. The normal leg made contact beneath the body and the involved one anterior to the body. The normal foot landed on the two distal rows of pads and then the proximal ones touched. The affected one landed on the two distal rows of pads and remained there.

W8R held the affected leg in slight retraction at the hip, extension at the knee, and ventriflexion at the ankle, with toes adducted and flexed loosely and listlessly. At contact both legs landed anterior to the body but the normal, which made contact first, was immediately placed beneath the body. Contact of the involved foot was made on the distal pads and on the heel and mid-solar pads. W9L resembled W8R save that the affected ankle was more ventriflexed and contact was made and maintained by the distal row of pads. The involved foot of both W9L and W8R was not moved back but remained anterior to the body.

W3L held the affected leg more retracted than protracted at the hip, more extended than flexed at the knee, and more ventriflexed than dorsiflexed at the ankle. The toes were loosely and listlessly flexed. There was no marked adduction, abduction, internal or external rotation. During descent it maintained this posture while the normal leg moved from protraction to retraction at the hip, to slight abduction

and external rotation, from flexion to extension at the knee, dorsiflexion to ventriflexion at the ankle, and the toes fanned. The animal landed on the two distal rows of pads. The involved foot landed passively on the distal rows of pads and then on the proximal ones as the whole leg simply flexed at all its joints. There were no postcontact adjustments made by the affected leg. When lifted from the floor there was no difference between the feet of W8R and W9L as to time of departure. W3L and W5L lost contact first with the affected foot.

(2) *Ventral Funiculus Lesion:* Both legs of W1L were held protracted at the hip, flexed at the knee, dorsiflexed at the ankle and somewhat inverted, with toes flexed. During descent the legs were more retracted at the hip, extended at the knee, and ventriflexed at the ankles, with toes slightly abducted. Contact was made on the distal rows of pads of both feet simultaneously. Both feet landed beneath the body. Postcontact adjustments were made normally by the involved leg. The affected ankle was more ventriflexed than normally. When raised from the supporting surface the normal leg usually maintained contact longer. After losing contact the affected leg was protracted at the hip, flexed at the knee, dorsiflexed and inverted at the ankle.

(3) *Combined Lateral and Ventral Funiculus Lesions:* W1R and W3L2 allowed the affected leg to hang more retracted than protracted at the hip, more extended than flexed at the knee, and ventriflexed at the ankle, with toes flexed and adducted. During descent the involved leg scarcely moved. The opposite foot made contact first while the affected one landed more anteriorly on the distal row of pads. The entire leg gave at all the joints as the body continued to descend after contact was made. When lifted from the floor the involved foot always lost contact first and was allowed to hang in the posture assumed before and during dropping.

(4) *Pyramidal Lesions:* The involved leg of both W7P and 510P was held more retracted than protracted at the hip, more extended than flexed at the knee, more ventriflexed than dorsiflexed at the ankle. There was adduction of the leg but no internal or external rotation. During descent this posture was maintained and contact was made on the distal and then on the proximal pads, after the normal foot had landed. There was no abduction or extension of the toes. No post-

contact adjustments were made with the abnormal leg. The affected foot always lost contact first as the animal was lifted.

(5) *Combined Pyramidal-Spinal Cord Lesions:* The affected leg of W7PC and of 510PC was held more retracted than protracted, more adducted than abducted at the hip, partially extended at the knee, and ventriflexed at the ankle but neither inverted nor everted. The toes and hallux of W7PC were flexed and adducted but the hallux of 510PC was extended. During descent the leg did not actively move. The foot made contact after the normal one, landing somewhat anteriorly and on the distal rows of pads. When the normal leg stepped back in postcontact adjustment the affected one sometimes followed. At times the involved foot of 510PC landed on top of the normal one. As the animals were lifted from the supporting surface the abnormal foot always lost contact first.

b) *Positive Supporting Reaction*

The following observations show that corticospinal tract lesions diminished the positive supporting reaction much more than did damage to extrapyramidal fibers.

(1) *Lateral Funiculus Lesions:* The response was present in the affected appendage of all four animals. It was only slightly decreased in strength in W5L, W8R, and W9L but scarcely elicitable in W3L.

(2) *Ventral Funiculus Lesion:* The response in the left leg of W1L was as easily elicited as normally and its strength was undiminished.

(3) *Combined Lateral and Ventral Funiculus Lesions:* Though the response was present in the right leg of W1R it was not elicitable in the affected appendage of W3L2.

Pyramidal Lesions: After the first few days both W7P and 510P showed a weak positive supporting reaction with the abnormal extremity.

Combined Pyramidal-Spinal Cord Lesions: Both W7PC and 510PC showed only a weak positive supporting reaction in the involved leg.

c) *Placing Reactions*

The following observations show that the placing reactions were affected only slightly if at all by extrapyramidal fiber damage but were markedly impaired by pyramidal fiber lesions.

(1) *Lateral Funiculus Lesions:* W8R, W9L, and W5L placed equally well and accurately with both legs. W5L did not grasp the table edge with the affected toes as he did at times with the normal ones. W3L responded with the unaffected leg whenever possible; the affected leg was used only if the movement required was slight. This response could be elicited by vision or contact with the same or opposite appendage.

(2) *Ventral Funiculus Lesion:* W1L placed well with the affected leg in response to both visual and contact stimulation.

(3) *Combined Lateral and Ventral Funiculus Lesions:* W1R placed first with the opposite leg when stimulated only by vision and the right one always followed. Tactile stimulation always elicited a placing response of the affected leg. W3L2, however, did not respond with the abnormal leg to any of these forms of stimulation. If the eyes were covered, tactile stimulation of the affected leg failed to cause placing of the normal extremity although proprioceptive stimulation did.

(4) *Pyramidal Lesions:* Neither W7P nor 510P responded to tactile stimulation with the leg opposite the lesion, although contact of the dorsum of the affected foot elicited a crossed placing reaction with the normal leg, showing therefore, that the defect was due to interruption of a descending motor tract and not to the interruption of an ascending sensory tract. Occasionally, when excited, these animals slightly protracted the abnormal leg in an effort at placing but were not successful even in response to proprioceptive stimulation.

(5) *Combined Pyramidal-Spinal Cord Lesions:* No appreciable difference in these tests was observed to occur after the operation upon the spinal cord (510PC and W7PC) was superimposed upon the pyramidal lesion (510P and W7P).

d) *Stepping Reactions*

The following observations show that impairment of the stepping reactions cannot be correlated with the degree of extrapyramidal fiber damage but can be correlated with the extent of the pyramidal fiber lesion. Paralysis due to a spinal cord lesion follows a definite pattern of distribution.

(1) *Lateral Funiculus Lesions:* (Forward). W8R and W9L stepped

forward equally well with both legs but W5L protracted the affected leg slightly higher than normally. W5L held the abnormal leg adducted at the hip, so that the toes caught on the opposite ankle. At each step the involved foot made contact only on the distal pads; the normal on both the distal and proximal pads. The steps taken by the affected appendage were somewhat shorter than those with the normal one. Initially W3L allowed the toes of the affected foot to drag on their dorsum with the foot slightly everted; subsequently he orientated them and stepped forward, though the step was appreciably shorter than normal.

(Backward). W8R did not contract the proximal musculature of the affected leg; the flexion of the knee which occurred never carried the abnormal leg past the position of the opposite leg. W9L moved the affected leg normally, except that the resulting step was shortened. W5L dragged the abnormal leg on the first step and then took short steps by protraction at the hip and flexion at the knee. This leg was so adducted at the hip that the foot scraped against the normal ankle at each step. W3L allowed the leg to drag passively, slightly protracted, extended at the knee, and ventriflexed at the ankle.

(To the side). The affected leg of W9L did not reach the midline during attempted adduction nor did it ever cross the opposite leg as occurs normally. Though abduction was performed the step was not as long as normal. W8R, when moved to either side, rotated the hip so that the affected leg was always protracted instead of adducted or abducted. W5L could not adduct the abnormal leg and attempted to rotate the pelvis in order to substitute a movement of protraction. He could abduct the leg but not as far as normally. W3L did not employ the affected leg when moved to either side.

(2) *Ventral Funiculus Lesion:* (Forward). The toes of the affected appendage of W1L orientated themselves normally. The leg was adducted and slightly internally rotated. Contact was made on the distal pads and movement did not seem impaired.

(Backward). The retraction of the involved leg was preceded by slight protraction but the degree of movement was not diminished.

(To the side). W1L adducted and abducted the affected leg normally.

(3) *Combined Lateral and Ventral Funiculus Lesions:* (Forward).

W1R stepped forward well although the right leg was markedly adducted. The toes folded listlessly so their dorsum rubbed the supporting surface until the latter phase of the step, when they orientated themselves and the weight was borne by the distal and proximal pads. W3L2 did not step with the involved leg. The toes flexed and the leg dragged passively.

(Backward). The right leg of W1R was not brought beneath the body. Most of the movement was made by flexion of the knee with the hip held in partial protraction. W3L2 allowed the left leg to drag partially retracted at the hip, and extended at the knee. The ankle was dorsiflexed and toes ventriflexed.

(To the side). Both legs of W1R were used well, crossing one another when stepping to either side. The right foot bore the weight on the distal and proximal pads while the left bore it on the distal ones. W3L2 made no effort to abduct or adduct the affected leg.

(4) *Pyramidal Lesions:* (Forward). The affected leg of 510P was externally rotated so that the adductors seemed to have a slight protracting action. The left hallux was held abducted and the leg sufficiently adducted so that this hallux frequently struck the opposite foot in moving forward. W7P dragged the affected leg retracted, slightly adducted and externally rotated at the hip, flexed at the knee, ankle everted and toes flexed. The medial surface of the foot and the dorsum of the toes maintained contact with the supporting surface.

(Backward). 510P and W7P held the affected leg partially retracted at the hip, extended at the knee, ankle dorsiflexed weakly, and toes flexed and adducted. There was slight flexion of the affected knee of 510P but the foot was never brought beneath the body.

(To the side). Neither W7P nor 510P showed any tendency to move the involved leg. It was dragged passively. When the body of W7P or 510P was moved to the contralateral side the leg dragged in a position of partial retraction and adduction at the hip, extension at the knee, ventriflexion and eversion at the ankle, with toes flexed. When moved to the ipsilateral side the leg dragged protracted and adducted at the hip, slightly flexed at the knee, ventriflexed and inverted at the ankle, with toes partially flexed.

(5) *Combined Pyramidal-Spinal Cord Lesions:* (Forward). The affected leg of W7PC was dragged retracted at the hip, flexed at the

knee, slightly abducted and externally rotated at the hip, everted at the ankle, and flexed at the toes, so that only the medial edge of the foot and the dorsum of the toes maintained contact with the ground. The pelvis of 510PC was held somewhat at an angle with the normal side forward in such a manner that the involved adductors had a slight flexing action and reinforced the protractors. The hallux was kept abducted and extended so that at each step it caught on the opposite heel. The second and fifth toes were adducted; the third and fourth abducted. They did not fold or drag on the floor. The foot was held parallel with the floor and sometimes even dorsiflexed. At times there was marked intention tremor in the leg as it was brought forward, but this was noticed only during periods of arousal and excitement and was not more accentuated at any one part of the movement than at another. At such times there was exaggerated protraction of the leg.

(Backward). 510PC retracted the affected leg slightly at the hip and flexed the knee, resulting in some backward movement but never enough to bring the leg beneath the body. After two or three such attempts the animal allowed the leg simply to drag. W7PC and usually 510PC allowed the leg to drag partially retracted at the hip, extended at the knee, and dorsiflexed and adducted but those of 510PC were more extended, with abduction between the third and fourth phalanges.

(To the side). When moved to the contralateral side the affected leg of 510PC showed slight adduction but it never crossed the other. The leg was not actively used but kept in adduction and retraction of the hip, extension of the knee, dorsiflexion of the ankle, extension of the toes, and abduction of the hallux and third and fourth phalanges. When moved in a similar direction W7PC allowed the affected leg to protract and abduct at the hip, flex or extend at the knee, evert and dorsiflex at the ankle with flexion of the toes, so that only the medial surface of the foot and the dorsum of the toes maintained contact with the floor. When moved to the ipsilateral side the affected leg of both monkeys dragged, retracted at the hip, flexed at the knee, inverted at the ankle, and with toes partially flexed, except the hallux of 510PC which remained extended. Only the lateral border of the foot remained in contact with the floor.

e) *Hopping Reactions*

The following observations show that the paretic muscles of the leg did not function as well in hopping as in stepping reactions.

(1) *Lateral Funiculus Lesions:* (Forward) W8R took a few hops with the right leg and then allowed it to drag passively. W9L made short hops with the left (affected) leg, maintaining the toes well orientated. W5L held the left leg off the ground protracted and adducted at the hip, flexed at the knee, and with ankle inverted and toes flexed. W3L allowed the left leg to drag behind the body passively.

(Backward and to the side). No one of these monkeys made an effort to move the affected leg. When moved toward the side opposite the lesion W5L held the abnormal leg beneath the body. The plantar surface maintained contact with the floor on the distal pads. The toes were slightly flexed.

(2) *Ventral Funiculus Lesion:* (Forward). No difference was noticed in the ability of W1L to use the left leg before and after operation. Twelve hops were made in covering a distance of six feet.

(Backward). Although the affected leg was handled in a normal manner two more hops were taken after operation in covering a distance of six feet than were taken before.

(To the side). When moved to the side opposite the affected leg the hip tended to rotate and the weight was borne on the distal pads. When moved to the side of the involved leg the latter was handled normally although the steps were slightly shorter than normal.

(3) *Combined Lateral and Ventral Funiculus Lesions:* (Forward). W1R, when hopping with the right leg, used the proximal muscles well, but the toes were allowed to flex and to drag their dorsum on the supporting surface until toward the end of the hop when they were normally orientated. W3L2 allowed the left (affected) leg to drag behind the body retracted and abducted at the hip, knee extended, ankle ventriflexed and everted, and phalanges partially flexed.

(Backward). Both W1R and W3L2 allowed their respective right and left legs to drag passively with the passive movement of the body.

(To the side). W1R, when hopping to the right, used the abductors well although the steps were somewhat shorter than normal. Although the ankle tended to invert passively during the first phase of the movement the plantar surface was placed with the weight on the distal and

proximal pads at the end of the hop. W3L2 allowed the leg to drag adducted and retracted at the hip, extended at the knee, ventriflexed and inverted at the ankle, and with toes flexed. When moved to the left or contralateral side W1R held the right leg adducted and partially protracted at the hip, knee partially flexed, with the plantarsurface maintaining contact on the distal and proximal pads. W3L2 allowed the leg to drag abducted and retracted at the hip, extended at the knee, everted and partially ventriflexed at the ankle, with the toes flexed.

(4) *Pyramidal Lesions:* (Forward). In both W7P and 510P the affected leg was dragged protracted at the hip, flexed at the knee, and ventriflexed at the ankle. In W7P the toes were flexed so that only their dorsum remained in contact with the ground. In 510P the hallux was abducted and partially extended. The toes were extended and the appendage simply held below the body, with slight external rotation.

(Backward). Both animals allowed the involved leg to drag retracted at the hip, extended at the knee, and ventriflexed at the ankle with the plantar surface in contact with the floor.

(To the side). The affected leg of each was handled as in the stepping movements.

(5) *Combined Pyramidal-Spinal Cord Lesions:* (Forward). In both animals the involved leg was handled as in stepping, except no attempt at use of either the adductors or protractors in protracting the leg was made by 510PC.

(Backward). Both W7PC and 510PC allowed the leg to drag partially retracted at the hip, extended at the knee, and ventriflexed at the ankle. The toes of W7PC were partially flexed and adducted at all joints. Those of 510PC were slightly extended and adducted, except between the third and fourth phalanges and the hallux where abduction was noted.

(To the side). W7PC, when moved to the normal side, allowed the leg to drag abducted and retracted at the hip, extended partially at the knee, ankle in midflexion, with the plantar surface in contact with the floor. The toes were flexed and adducted. 510PC maintained the leg adducted and retracted at the hip, partially extended at the knee, ankle dorsiflexed with toes extended, and plantar surface maintaining contact.

f) *Voluntary Movements*

The following observations show that paralysis resulting from a lesion in the spinal cord can be correlated in degree with corticospinal fiber damage only. In general the phasic activity of the small distal muscles was affected most by the interruption of these fibers. Paralysis due to a spinal cord lesion followed a definite pattern of distribution. Extrapyramidal fiber lesions were associated with a *reluctance* to use the affected muscles.

(1) *Lateral Funiculus Lesions:* Except for the preference shown in using the normal leg and the tendency to initiate movement with it, no differences between the voluntary use of the normal and the affected sides of W5L, W8R, and W9L were observed. W3L allowed the involved leg to assume awkward positions. In stepping up, the normal leg was raised first and most of the body weight was supported simultaneously by grasping the side of the cage with a hand. Stepping forward with the affected leg was observed but the steps were short and the toes and foot dragged ventriflexed. In stepping back a slight flexion of the knee was occasionally observed. When moving to either side W3L placed his weight on his hands and hopped on the good leg, allowing the other to drag, until the final position was attained and then the leg was orientated in relation to the body. Occasionally the affected leg was abducted before the weight of the body shifted to that side. He hung the involved toes over the cage wires but never grasped with them.

(2) *Ventral Funiculus Lesion:* No alteration in the voluntary use of the affected leg was seen in W1L. However, when the opportunity of choice presented itself, preference for the use of the normal leg and foot was always shown.

(3) *Combined Lateral and Ventral Funiculus Lesions:* W3L2 did not use the affected leg in stepping forward, backward, or to the side. This leg dragged passively. W1R used the right leg without hesitation or fumbling. There was no limitation of movement but there was loss of strength. No tremor was noted. Occasionally the animal would grasp the wires of the cage with the right toes. Grooming and scratching movements were well performed.

(4) *Pyramidal Lesions:* W7P and 510P usually showed a preference for the use of the normal leg. When stepping up, either the normal

or affected foot might be lifted first, but frequently the latter struck its dorsal surface on the ledge. At times the weight of the animal was supported on the affected leg but only for a brief period. The involved foot was never used for scratching. Eversion of the ankle was never seen, and dorsiflexion only during excitement. When moving forward the leg either protracted greatly or to such a slight degree that the toes were allowed to drag on their dorsal surfaces, with the foot ventriflexed. When moving toward the affected side the leg abducted before a shift in body weight occurred. Instead of moving sideways the animals preferred turning and moving forward. When moving to the side opposite the affected leg the latter was simply dragged and then adducted and protracted at the hip, and flexed at the knee, in such a manner as to bring it beneath the body. Most of the weight borne by the involved foot was placed on the heel pad, the distal pads resting lightly on the surface. The toes and hallux were at times hooked weakly about the wire of the cage. No tremor was noted. The affected extremity was occasionally left in awkward positions.

(5) *Combined Pyramidal-Spinal Cord Lesions.* Neither W7PC nor 510PC showed any change in the status of their spontaneous voluntary movements which was not noted after the pyramidal lesion. The extent, accuracy, strength, and range of movement of the pyramidal-spinal cord preparations were not different from those of the pyramidal preparations. However, one important distinction was present. Although both pyramidal animals frequently showed a preference for the use of the normal leg, such preference was always shown after the cord operation had severed extrapyramidal fibers.

g) *Associated Movements*

The following observations show that associated movements were exaggerated after isolated pyramidal fiber damage. They were diminished or abolished by extrapyramidal fiber lesions.

(1) *Spinal Cord Lesions:* Exaggeration of associated movements was not observed in any of these animals except W3L. W5L and W1L showed much less associated movement in the affected appendage than characterizes the normal. W3L2 had no such reactions. The associated movements performed by W3L were similar to those observed in the pyramidal preparations.

(2) *Pyramidal Lesions:* In both W7P and 510P tonic and phasic

associated movements were seen. When the normal leg was protracted, externally rotated, flexed at the knee, inverted and ventriflexed at the ankle, the affected leg retracted at the hip, extended at the knee, inverted and ventriflexed at the ankle. Occasionally the affected leg mirrored the purposive movement of the normal one. At other times the tonic alteration of position at each involved joint was the reciprocal of the postural alteration of the normal ones. When scratching with the normal leg occurred, the abnormal extremity protracted slightly at the hip, flexed at the knee, inverted at the ankle, flexed and adducted at the phalangeal joints, and more or less rhythmically but ineffectively waved in the air in a scratching-like motion.

(3) *Combined Pyramidal-Spinal Cord Lesions:* Neither W7PC nor 510PC had associated movements, although both had shown exaggeration of them prior to the second or spinal cord operation.

h) *Atrophy*

The following observations show that pyramidal fiber damage caused atrophy mainly in the distal muscles. Extrapyramidal fiber lesions were followed by atrophy predominantly in the proximal muscles.

W8R, and W9L were not kept alive long enough to make observations that would be significant for determination of the presence of atrophy, nor was W1 following the second operation (W1R). Only the abnormal extremities of W7P, 510P, and W5L were comparable, as was also the left leg of W1. There was a greater degree of atrophy of the distal musculature of the pyramidal preparations than of the distal musculature of the spinal cord animals. However, the degree of atrophy in the proximal muscles of the latter (W1L and W5L) was more marked than that in the proximal muscles of the pyramidal animals. The degree of atrophy in W1L and W5L was out of proportion to the degree of motor involvement. However, a long period elapsed, over a year and a half, between the operations and the final measurements. In this time both animals grew to about twice their weight at operation, and although little if any paresis was observed, both showed a definite preference for the use of the normal leg.

SUMMARY OF IMPAIRMENT OF USE OF MUSCLES

The degree of paralysis in all of these animals varied directly with the degree of damage to the corticospinal fibers. The greater that

damage, the weaker the positive supporting reaction, and the more impaired the "magnet" and placing reactions. In general the more distal the musculature the greater was the loss of control after injury to these fibers. Within the divisions of proximal and distal musculature the paralysis was selective. The retractors and adductors of the hip, the flexors of the knee, the dorsiflexors of the ankle and the toes, and the evertors of the ankle suffered more than their antagonists. The interruption of nerve fibers lying superficial to the lateral corticospinal tract does not contribute to the degree of impairment of phasic activity. The amount of damage to the lateral corticospinal tract was greater in W8R and W9L than in W1R, while that to the superficial fibers was greater in W1R, yet W1R retained better control of the affected leg than did either W8R or W9L.

A spinal cord lesion in the lateral funiculus superimposed upon surgical interruption of a pyramid did not increase impairment of phasic activity, evaluated by amount, accuracy, strength and range of movement. This is indeed remarkable for these particular spinal cord lesions added interruption of the lateral reticulospinal, rubrospinal, and spinocerebellar fibers to the existing damage of the pyramidal tract. However, *preference* for the use of the affected extremity was markedly diminished after the second operation.

The observations in the first part of the above paragraph together with the fact that paralysis was increased in W3L2 after a lesion in the ventral funiculus was added to one in the lateral corticospinal tract suggests the presence in this funiculus of a fiber tract which makes a contribution to control of phasic activity (ventral corticospinal tract).[3] Contact stimulation alone of the abnormal leg of W3L2 did not cause a placing response of the normal leg. Perhaps tactile impulses do not ascend in the dorsal funiculus.

Associated movements were observed in both pyramidal preparations (W7P and 510P) and in one spinal cord lesion (W3L), where the damage was confined to the site of the lateral corticospinal and dorsal spinocerebellar tracts. These associated reactions were abolished in all three by subsequent injury to extrapyramidal systems within the spinal cord. In those monkeys, in which there was initial injury to extrapyramidal tracts (W1L and W5L) associated reactions were markedly diminished.

The atrophy of skeletal muscle determined by measurement of the

circumference of the lower extremity was greater in the distal musculature of the pyramidal preparations than in the proximal musculature. On the other hand in those spinal cord preparations where the damage was greater to extrapyramidal systems the atrophy was more marked in the proximal musculature of the affected extremity.

CHART I

*Atrophies**

CIRCUMFERENCE OF LEG MEASURED AT DIFFERENT LEVELS	LEFT	RIGHT	PERCENTAGE ATROPHY
Examined 89 days after operation			
	cm.	*cm.*	*per cent*
510P			
Metatarsals	6.5	7.3	10.9
1 cm. above malleoli	7.8	8.0	2.5
3 cm. below tibial tubercle	11.0	11.7	6.4
3 cm. above knee	13.2	14.0	5.7
6 cm. above knee	16.0	16.5	3.0
Examined 89 days after operation			
W7P			
Metatarsals	7.8	8.5	8.1
Above int. and ext. malleoli	8.0	8.5	5.8
3 cm. below tibial tubercle	12.5	13.5	7.4
3 cm. above knee	15.8	16.2	2.4
6 cm. above knee	16.4	17.0	2.7
Examined 19 months after operation			
W1L			
Metatarsals	7.6	8.0	5.0
1 cm. above malleoli	8.6	9.0	4.4
3 cm. below tibial tubercle	12.5	13.8	9.4
3 cm. above knee	15.5	16.8	7.1
6 cm. above knee	17.0	19.0	10.5
Examined 20 months after operation			
W5L			
Metatarsals	7.8	8.0	2.5
1 cm. above malleoli	8.5	9.0	5.5
3 cm. below tibial tubercle	11.7	12.5	5.6
3 cm. above knee	14.5	16.0	9.3
6 cm. above knee	16.0	18.0	11.1

* The limitations of the term "atrophy" as used here are mentioned above.

The function of the muscles of progression made paretic by central nervous system lesions was better during stepping than hopping and best during voluntary movement. The essential difference between these functions is the number of muscles employed. The use of such a paretic muscle apparently becomes progressively more effective as the number of other muscles employed simultaneously and in a coordinated manner increases.

2) ALTERATION IN MUSCLE TONE

a) *Resistance to Passive Movement*

The observations recorded in this section show that interruption of the corticospinal fibers was followed by hypotonicity. Hypertonicity of the affected muscles can be correlated only with reticulospinal fiber lesions. Damage simultaneously or previously to other descending fibers disguised or at times completely obscured this relationship of the reticulospinal fibers to hypertonicity.

(1) *At Hip. Lateral Funiculus Lesions:* W3L had a decreased degree of resistance to all passive movements at the hip. W8R had a resistance increased for retraction, abduction, and external rotation, decreased for protraction, and no alteration for adduction or internal rotation. The adductor longus of the affected leg was prominent and to palpation felt much more tonic than the normal muscle. The involved retractors, protractors, abductors, external and internal rotators of W9L showed no change, but there was increased resistance to abduction. W5L had no increased resistance to protraction, adduction or internal rotation, a continuous and marked resistance to retraction at the hip after the first 20 degrees, and an increased amount for abduction and external rotation.

Ventral Funiculus Lesion: W1L showed decreased resistance to protraction and adduction, and only slight but increased resistance to external rotation, to abduction, and to retraction after the first 30 degrees. When the leg was greatly retracted there was resistance due to contracture.

Combined Lateral and Ventral Funiculus Lesions: W1R showed decreased resistance to protraction, retraction, adduction, and internal rotation of the right hip, but increased and constant resistance to abduction and external rotation. That of W3L2 was consistently decreased.

Pyramidal Lesions: In W7P and 510P resistance was decreased for all movement except that to abduction, and that was increased and constant throughout the arc of movement.

Combined Pyramidal-Spinal Cord Lesions: W7PC and 510PC had moderate and constant resistance to retraction, very little to protraction, and decreased resistance to adduction. That to external rotation and abduction was greater than normal.

(a) *At Knee. Lateral Funiculus Lesions:* W3L showed decreased resistance to flexion and to extension of the knee. W8R had a definite palpable lengthening reaction and clasp-knife quality in the extensors during flexion. Simultaneously there was a definite shortening reaction in the semimembranosus. Resistance to extension was only slight. Tremor could be palpated in the quadriceps femoris. Increased resistance to flexion associated with a palpable knotting of the quadriceps femoris was observed in W9L, while that to extension was decreased. W5L had a slightly increased resistance to flexion through the first 90 degrees, at which point the resistance suddenly gave with a clasp-knife quality. There was a little resistance to extension.

Ventral Funiculus Lesion: W1L showed only the normal resistance to both flexion and extension.

Combined Lateral and Ventral Funiculus Lesions: W1R had little resistance to flexion or extension of the right knee. However, when the right knee was almost completely extended, a sudden resistance of inflexible quality appeared, due not to increased tone but rather to a contracture of the hamstrings. Resistance to extension and to flexion of the left knee was decreased in W3L2.

Pyramidal Lesions: In W7P and 510P, resistance to passive extension and flexion of the left knee was decreased.

Combined Pyramidal-Spinal Cord Lesions: 510PC showed an increase with clasp-knife quality to flexion of the left knee; while none was observed in W7PC. No resistance to extension was found in W7PC or 510PC until the abnormal knee was almost fully extended. At this point a sudden rigid resistance was present due to shortening of the hamstring musculature.

(3) *At Ankle. Lateral Funiculus Lesions:* Resistance to all movements of the left ankle was decreased in W3L; unchanged in W9L. W8R had a slight increase of resistance to dorisflexion and to eversion

of the right ankle, a slight decrease to ventriflexion, and to inversion. A slight increase to dorsiflexion of the left ankle was observed in W5L. A certain rigid resistance was met when the terminal portion of the arc of this movement was attained. (See Contractures.) No alteration in resistance to inversion or eversion was found in this monkey, while that to ventriflexion was decreased.

Ventral Funiculus Lesion: W1L displayed an increased resistance to dorsiflexion, as a result of contracture of the ventriflexors of the ankle and toes, and decreased resistance to ventriflexion of the left ankle. Increased resistance to both inversion and eversion of the left ankle in this monkey resulted from contracture.

Combined Lateral and Ventral Funiculus Lesions: Resistance was decreased to inversion and ventriflexion and unchanged to dorsiflexion and eversion of the right ankle in W1R. W3L2 did not show any resistance to any movement of the left ankle.

Pyramidal Lesions: Decreased resistance to ventriflexion, inversion, and eversion of the left ankle was observed in both W7P and 510P. Although there was no increase in tone of the gastrocnemius-soleus, shortening of that muscle group caused resistance toward the latter part of the arc of movement.

Combined Pyramidal-Spinal Cord Lesions: W7PC and 510PC exhibited an increased degree of resistance to eversion and dorsiflexion of the left ankle but no increase to ventriflexion and inversion.

(4) *At Metatarsophalangeal and Phalangeal Joints. Lateral Funiculus Lesions:* Decreased resistance to all movements of the involved toes was observed in W3L and W8R. W9L showed no alteration in degree of resistance to abduction or adduction of the toes of the left foot and a decreased resistance to their ventriflexion. (See Contractures.) W5L showed no alteration for abduction or adduction, a decreased amount for ventriflexion, but marked resistance to dorsiflexion (See Contractures).

Ventral Funiculus Lesion: W1L showed only normal resistance to movements of the digits of the left foot except to dorsiflexion. The increased resistance to that movement was due to contracture of the flexors.

Combined Lateral and Ventral Funiculus Lesions: W3L2 and W1R showed a less than normal degree of resistance to all movements except

that to dorsiflexion, for the flexors of the toes of the abnormal extremity were shortened.

Pyramidal Lesions: W7P and 510P exhibited less resistance to all movements of the digits of the left foot than normal. 510P however, showed some resistance to adduction of the affected hallux. (See Contractures.)

Combined Pyramidal-Spinal Cord Lesions: 510PC and W7PC displayed no increased resistance to ventriflexion or to abduction of the toes of the abnormal foot. 510PC showed an increased degree of resistance to adduction of the affected hallux, and both of these monkeys had a greater than normal degree of resistance to dorsiflexion of these digits, an increase not entirely due to contracture.

b) *Tendon Reflexes*

The following observations show that interruption of corticospinal fibers caused high threshold reflexes of sluggish response. Brisk, low threshold, irradiating tendon reflexes with decreased arc of movement can be correlated only with lesions of the reticulospinal fibers. Interruption of other descending spinal cord fibers disguised this relationship of the reticulospinal tracts to a particular type of tendon reflex.

(1) *Extensors of Affected Knee. Lateral Funiculus Lesions:* The tendon reflexes of the affected extremity in W5L and W8R were lowered in threshold, increased in briskness, and decreased in arc of movement. Those of W9L were normal although tapping the normal knee caused irradiation to the opposite or affected adductor longus. The response of the left quadriceps femoris in W3L was sluggish, pendular, and higher in threshold than normal.

Ventral Funiculus Lesion: In W1L the response of the left extensors of the knee was very brisk, lower in threshold and of more brief duration than normal. There was irradiation to the right adductor longus.

Combined Lateral and Ventral Funiculus Lesions: The response to tapping the patellar tendon of the affected leg in W1R and W3L2 was sluggish and pendular. The threshold was elevated.

Pyramidal Lesions: The response of this muscle in W7P and 510P was sluggish and pendular and the threshold elevated.

Combined Pyramidal-Spinal Cord Lesions: In 510PC the patellar

reflex showed a lower threshold and a more brisk response. In W7PC it remained unchanged. In both animals this tendon reflex irradiated to the opposite (normal) adductor longus.

(2) *Flexors of Affected Knee. Lateral Funiculus Lesions:* The response of the flexors of the knee was brisk and of brief duration in both W5L and W8R and the threshold was lowered. In W9L the threshold of this tendon reflex was lower than normal but the contraction of the muscles was not brisk. On the other hand in W3L the response was sluggish and the threshold elevated.

Ventral Funiculus Lesion: In W1L the threshold was lower and the response more brisk and of shorter duration than normal.

Combined Lateral and Ventral Funiculus Lesions: In both W1R and W3L2 the response was sluggish and pendular. The threshold was elevated.

Pyramidal Lesions: Similarly, W7P and 510P showed sluggish, pendular responses and elevated thresholds.

Combined Pyramidal-Spinal Cord Lesions: The thresholds for this tendon reflex in W7PC and 510PC were markedly lowered and the responses very brisk and of brief duration.

(3) *Tendon of Achilles. Lateral Funiculus Lesions:* The thresholds of this tendon reflex in W5L was lower than normal and the response, which was more brisk, irradiated to the left hamstrings. In W9L and W8R the response was more brisk than the normal. On the other hand in W3L the threshold of this reflex was raised and the response sluggish.

Ventral Funiculus Lesion: The threshold of response to tapping the left Achilles tendon of W1L was lower than normal, and the contraction of the M. gastrocnemius was brisk, recruiting the ipsilateral hamstring muscles.

Combined Lateral and Ventral Funiculus Lesions: In both W3L2 and W1R the threshold for the Achilles jerk was elevated and the response was more sluggish and pendular than normal.

Pyramidal Lesions: W7P and 510P showed elevated thresholds and slow and pendular responses.

Combined Pyramidal-Spinal Cord Lesions: In both W7PC and 510PC the tendon reflex was more brisk and the threshold lower than normal.

(4) *Tibialis Anterior. Lateral Funiculus Lesions:* The threshold of the tendon reflex of M. tibialis anterior was lower than normal in W5L,

W9L, and W8R, while the response was particularly brisk in the latter two. This reflex was not elicited in W3L.

Ventral Funiculus Lesion: This reflex was not elicited in W1L either before or after the operation.

Combined Lateral and Ventral Funiculus Lesions: W3L2 and W1R never gave a response after their operations although before, the tendon reflex of the M. tibialis anterior was present.

Pyramidal Lesions: The myototic reflex of the tibialis anterior was observed in W7P even after the operation and present both before and after in 510P. In both the threshold was higher and the response more sluggish than it was before operation.

Combined Pyramidal-Spinal Cord Lesions: In both W7PC and 510PC the threshold of this tendon reflex was lower than normal.

(5) *Ventriflexors of Toes. Lateral Funiculus Lesions:* After operation the threshold was lowered and the response more brisk in the ventriflexors of the toes of W5L, W8R and W9L. The response of these muscles in W8R recruited the proximal muscles. This reflex was not elicited in W3L.

Ventral Funiculus Lesion: The ventriflexors of the toes in W1L had a lower threshold and a more brisk response than normal. There was irradiation to the ipsilateral hamstring muscles.

Combined Lateral and Ventral Funiculus Lesions: This reflex was not elicited in W1R and W3L2.

Pyramidal Lesions: This tendon reflex was not present either in W7P or in 510P.

Combined Pyramidal-Spinal Cord Lesions: Both W7PC and 510PC had a reflex of normal briskness and the threshold in the latter was lower than that of the normal toes of the opposite foot.

c) *Tremor and Clonus*

The following observations show that some extrapyramidal fiber lesions caused tremor and clonus but pyramidal fiber lesions did not.

Lateral Funiculus Lesions: W5L showed dorsiflexion and marked tremor of the second toe following a moving stimulus on the plantar surface. Tremor of the quadriceps femoris and adductor longus on passive movement was noted in W5L and W8R. W9L and W3L did not show either tremor or clonus.

Ventral Funiculus Lesion: W1L showed clonus in the ventriflexors when the foot was dorsiflexed.

Combined Lateral and Ventral Funiculus Lesions: No clonus was observed in W3L2 or on the right in W1R.

Pyramidal Lesions: None occurred in W7P or 510P.

Combined Pyramidal-Spinal Cord Lesions: No clonus or tremor on passive movement was observed in W7PC or 510PC.

d) *Contractures*

The following observations show that contractures were usually more extensive and severe after extrapyramidal than after pyramidal fiber lesions. Certain muscles were affected more frequently than others so that the distribution of contractures followed a more or less definite pattern.

Lateral Funiculus Lesions: W8R, W3L, and W9L did not have contractures. W5L had contractures of the adductors and protractors of the hip, flexors of the affected knee, and the ventriflexors of the ankle and of the toes.

Ventral Funiculus Lesion: Contractures of the protractors of the hip, flexors of the knee, ventriflexors of the ankle and toes, and invertors and evertors of the ankle were found in W1L.

Combined Lateral and Ventral Funiculus Lesions: W3L2 and W1R had contractures of the flexors of the knee, and ventriflexors of the ankle and toes.

Pyramidal Lesions: W7P and 510P had slight contracture of the affected adductors and of the ventriflexors of the ankle and toes.

Combined Pyramidal-Spinal Cord Lesions: W7PC and 510PC had shortening of the flexors of the knee, ventriflexors of the ankle and toes, invertors of the ankle, as well as increased contracture of the adductors of the hip.

SUMMARY OF ALTERATION IN MUSCLE TONE

Maximal damage to the lateral corticospinal tracts (W3L, W7P and 510P) with little or no injury to extrapyramidal systems was followed by sluggish pendular tendon reflexes and a generalized hypotonia. The adductors of the thigh in the pyramidal preparations (W7P and 510P) were an exception for they were hypertonic. Further, hypotonia pre-

dominated (internal rotators and adductors of hip were exceptions) when the spinocerebellar (W1R) and vestibulospinal tracts were injured with only slight damage to the lateral corticospinal tract.

Extensive infringement upon the extrapyramidal fibers in the lateral funiculus (site of reticulospinal and rubrospinal tracts) yielded increase in tone and brisk tendon reflexes with irradiation to proximal muscles (W5L, W8R, and W9L). Resistance to passive movement of these hypertonic muscles was occasionally accompanied by lengthening and shortening reactions (W8R, W9L). Severing the lateral funiculus in the pyramidal preparations changed the hypotonic paresis to a spastic one (510PC, W7PC). Where the vestibulospinal tract was also cut (W7PC), the tendon reflexes were hyperactive but the hypertonicity was not as great. Supporting this finding, briskness of tendon reflexes unrelated to hypertonia followed cutting the superficial fibers of the ventral funiculus (ventral reticulospinal and vestibulospinal) in W1L. Moreover, if a lesion, confined to the lateral funiculus, damaged the lateral corticospinal fibers as well as those lying medial and lateral to them neither hypertonia nor brisk tendon reflexes were present (W3L).

In other words, minimal damage to the corticospinal tract plus maximal damage of the extrapyramidal fibers found in the lateral funiculus yielded minimal paralysis and maximal hypertonia and hyperactive tendon reflexes which recruited more proximally lying muscles. An isolated lesion of the ventral funiculus produced minimal hypertonia but hyperactive tendon reflexes (W1L). Interruption of the lateral corticospinal tract either at the pyramids or in the spinal cord produced paralysis and hypotonia. Addition of extrapyramidal fibers to the pyramidal lesion changed the hypotonia to hypertonia, and the sluggish pendular reflexes to low threshold, brisk, irradiating ones. However, damage to fibers lying deeper in the spinal cord (W3L2) completely masked the hypertonia and hyperactive reflexes.

In general the hypertonicity which followed the cutting of extrapyramidal fibers in the lateral funiculus showed a selective pattern of distribution. The protractors, adductors, and internal rotators at the hip were more affected than the retractors, abductors, and external rotators; the extensors of the knee more than the flexors; and ventriflexors and invertors of the ankle more than the dorsiflexors and everters. This is the characteristic pattern of hypertonia following abla-

tion of 4s or of total area 4 in the frontal lobe of the macaque. The variations of this pattern will be mentioned in the discussion.

Tremor and clonus followed only extrapyramidal lesions (W5L, W8R, W1L).

Contractures occurred in a more or less definite pattern; the flexors of the knee, adductors and protractors of the hip, ventriflexors of the ankle and toes, and invertors of the ankle being most frequently affected. Although slight contracture of the adductors of the hip and ventriflexors of the ankle and toes followed pyramidal sectioning, subsequent extrapyramidal damage increased the degree and also caused contracture of the knee flexors and invertors of the ankle. Contractures occurred in hypotonic (W1R, W3L) as well as hypertonic muscles (W5L, W1L) and were more extensive following extrapyramidal lesions than pyramidal ones. Some hypertonic muscles (extensors of the knees) did not show contracture.

3) SUPERFICIAL REFLEXES

The following observations show that superficial reflexes were affected most by corticospinal fiber damage. Brisk adduction of the affected hallux on pinching the terminal phalanx of the middle toe was characteristic after isolated extrapyramidal lesions.

a. *Abdominal Reflex. Lateral Funiculus Lesions:* The threshold of the abdominal reflex was unchanged in the upper or lower affected quadrants of W5L. W9L showed an elevated threshold for this reflex in the affected lower quadrant but a normal response in the upper. In W8R this reflex was absent in the lower quadrant and present in the upper one only to vigorous scratching of the skin. W3L gave no response in either quadrant.

Ventral Funiculus Lesion: The abdominal reflex was normal in W1L.

Combined Lateral and Ventral Funiculus Lesions: This superficial reflex was absent on the affected side in W3L2 and in the lower quadrant in W1R. The latter animal, however, gave a slight response to vigorous stimulation in the upper quadrant.

Pyramidal Lesions: No response was elicited in the affected upper or lower quadrants of either W7P or 510P.

Combined Pyramidal-Spinal Cord Lesions: No response on the affected side occurred in W7PC or 510PC.

b. *Cremasteric Reflex: Spinal Cord Lesions:* The threshold of the

cremasteric reflex was higher on the affected side of W9L than it was on the normal side; but in both the W3L and W3L2 preparations it was abolished.

Pyramidal and Combined Pyramidal-Spinal Cord Lesions: No response could be elicited by stroking the skin over the adductors of the normal or affected side of W7P, W7PC, 510P or 510PC.

c. *Plantar Reflex. Lateral Funiculus Lesions:* Scratching the lateral border of the plantar surface of the left foot was frequently followed by extension and fanning of the toes after the operation in W5L. Marked extension and fanning of the toes of the right foot and extension at the metatarsophalangeal joints with the interphalangeal joints held in flexion on the left occurred in W8R. In W9L the toes of each foot showed extension at the metatarsophalangeal joints followed by flexion, the interphalangeal joints remaining in flexion. W3L showed ventriflexion of the interphalangeal and metatarsophalangeal joints on both sides.

Ventral Funiculus Lesions: After operation the flexion of the toes and maintenance of adduction associated with dorsiflexion of the left foot in W1L was changed to extension and slight abduction of the toes.

Combined Lateral and Ventral Funiculus Lesions: Both W3L2 and W1R showed extension and fanning of the affected toes.

Pyramidal Lesions: In W7P the response was similar on the two sides, namely, flexion of the toes, dorsiflexion of the foot, and slight withdrawal. 510P gave flexion of the toes, dorsiflexion of the foot, and slight withdrawal on the normal side: slight extension at the metatarsophalangeal joints with maintenance of flexion of the interphalangeal ones, dorsiflexion at the ankle, and withdrawal on the affected side.

Combined Pyramidal-Spinal Cord Lesions: W7PC showed no response on the affected side. The response given by 510PC was similar to that of 510P.

d. *Pinching Terminal Phalanx of Middle Toe. Lateral Funiculus Lesions:* Increased briskness and degree of adduction of the affected hallux followed pinching the terminal phalanx of the middle toe in W8R, W9L, and W5L. No alteration of the normal degree of adduction was observed in W3L.

Ventral Funiculus Lesion: The affected hallux of W1L showed an

exaggerated response—usually one of adduction with flexion but occasionally adduction with extension.

Combined Lateral and Ventral Funiculus Lesions: The affected hallux of W3L2 gave no response to tweeking of the middle toe; that of W1R showed slight flexion and adduction.

Pyramidal Lesions: Response of the affected hallux was absent in both W7P and 510P.

Combined Pyramidal-Spinal Cord Lesions: W7PC showed sluggish extension of the affected hallux. 510PC gave no hallux response.

SUMMARY OF SUPERFICIAL REFLEXES

The greater the infringement of the lesion on the lateral corticospinal area the more impaired were the abdominal reflexes (W3L, W3L2, W7P, W7PC, 510P, 510PC). The lower quadrant was consistently more affected than the upper (W8R, W1R). Although in one animal the spinothalamic tracts were partially severed (W1L) no alteration in the reflex occurred. Severing extrapyramidal fibers (W1L, W5L, W9L) has little effect upon this reflex. Extensive pyramidal tract damage abolishes the abdominal reflex as well as the cremasteric reflex.

Both extension with fanning of the toes (510P) and ventriflexion of the toes (W3L, W7P) occurred in animals with extensive lateral corticospinal tract damage. In those animals with predominantly extrapyramidal fiber damage (W5L, W8R, W9L, W1L), if there was any change in the normal response, it was extension of the metatarsophalangeal joints and occasionally abduction or fanning of the toes.

Exaggeration of the adductor response of the hallux on pinching the middle toe usually occurred with extrapyramidal damage (W8R, W9L, W5L, W1L). However, if the lesion was too superficial to involve much of the reticulospinal fiber area (W1R) or if the corticospinal tract was extensively severed (W3L, W7P, 510P) there was no exaggerated adduction of the hallux; and subsequent extrapyramidal fiber lesions (W7PC, 510PC, W3L2) in such animals did not cause an exaggeration of it.

SUMMARY OF RESULTS

In the macaque extensive injury to the corticospinal tract raised the threshold of all reflexes and produced a general hypotonic paresis.

The latent period of the tendon reflexes was lengthened and their response sluggish. All of the superficial reflexes were diminished in their response. The plantar reflex was not consistently changed to a single pattern type. In the two pyramidal preparations (W7P, 510P) the contralateral adductors were hypertonic, and the degree of paralysis and atrophy was greater in the distal musculature. The pattern of the paresis, however, was selective, choosing for greater loss in phasic activity the retractors and adductors of the hip, flexors of the knee, dorsiflexors of the ankle and toes, and evertors of the ankle. Slight contractures in the adductors of the thigh and ventriflexors of the ankle and toes and exaggerated associated movements completed the findings. No clonus or tremor was observed.

Lesions in the lateral and ventral funiculi which injured the areas occupied by the reticulospinal tracts (W5L, W8R, W9L, W1L) was followed by a selective hypertonicity, occasionally clasp-knife in quality, brisk irradiating tendon reflexes, lengthening and shortening reactions, clonus, and contracture. Increase in tone was more marked in the protractors and adductors of the hip, extensors of the knee, ventriflexors and invertors of the ankle, and ventriflexors of the toes—a pattern unlike that for the distribution of paralysis in corticospinal tract lesions. The pattern of contracture, however, did not follow exactly that of increased tone; for shortening occurred most frequently in the protractors and adductors at the hip, the flexors of the knee, the ventriflexors and invertors of the ankle and the ventriflexors of the toes. Paresis was negligible; for when the reluctance to use the affected extremity was overcome phasic activity was seen to be only slightly altered (W5L, W1L). Atrophy of the musculature of the lower extremity was greater in the proximal muscles (W5L, W1L). Associated reactions were either not observed or diminished. Indeed the exaggeration of associated movements resulting from surgical interruption of one pyramid was abolished by severing these extrapyramidal fibers (W3L2, W7PC, 510PC). And this second lesion superimposed certain components of spasticity upon the hypotonic paresis of the pyramidal preparations (W7PC, 510PC).

Injury to the superficial fibers of the ventral funiculus (reticulospinal and vestibulospinal) (W1L) yielded brisk tendon reflexes with low thresholds. Tone was only slightly increased proximally. Con-

tractures occurred and were most marked in some of the more distal muscles.

The threshold of the superficial reflexes was raised by lesions of the pyramidal tract (W7P, 510P, W3L). Superficial reflexes were less affected by extrapyramidal fiber damage (W5L, W9L, W1L). The plantar response was more likely to have an extensor and fanning phase with the latter lesions. Of the superficial reflexes, exaggerated adduction of the hallux produced by pinching the middle toe was the most consistent and characteristic response following isolated extrapyramidal lesions (W1L, W8R, W9L, W5L).

Discussion

The evaluation of the results of surgical division of nerve fibers in the spinal cord presents three questions for consideration: 1) the fiber groupings which were severed and their relations to the corticifugal systems, 2) the types of loss of normal function, and 3) the allocation of these functional losses to specific fiber systems. The first question can be answered with some degree of accuracy by using the present and previous studies of fiber tracts in the spinal cord of the macaque and by considering the relation of the termination of corticifugal systems with the nuclei of origin of the descending spinal cord systems. The second and third questions only require application of present knowledge to the physiological and histological examinations.

The lesions in this series, caused by surgical division of the spinal cord of the macaque, were limited to the lateral and ventral funiculi. Within the ventral funiculus at the level of surgical division (T7 or T8) the known descending systems are the vestibulospinal and the reticulospinal. The ventral corticospinal tract at this level is negligible though present.[3] Within the lateral funiculus the known descending tracts are the frontospinal,[4] the parietospinal, the rubrospinal, and the

[4] "Pyramidal" and "corticospinal" are used synonymously in this paper. In the Macaque (Macaca mulatta) Peele (13) found that nerve fibers degenerated in the pyramids and in that region of the lateral funiculus assigned to the corticospinal tract subsequent to the removal of the parietal lobe. Therefore nerve fibers within the pyramids and within the corticopsinal tract stem from the parietal as well as the frontal lobe. These two systems are designated respectively as the parietospinal tract and the frontospinel tract.

reticulospinal. Furthermore, the effect of severing the ascending systems must be considered,—in the ventral funiculus, the ventral spinothalamic tract; in the lateral funiculus, the lateral spinothalamic and the dorsal and ventral spinocerebellar tracts. The proprioceptive systems of the dorsal funiculus remained intact and furnished a route for tendon, joint, and muscle sense to the cortex cerebri. Although the lateral and ventral spinothalamic tracts were partially severed in some of these animals, the route for touch impulses, which is described for man as traveling in the dorsal funiculus, was open. Therefore, if this is a fact for the monkey (see Summary of Impariment of Use of Muscles) the long afferent side of the arc for testing superficial reflexes was present. Pain mediating fibers seemed to escape even in those monkeys in which lesions were bilateral.

The cortical areas which seem to be specifically related to the fiber systems of the spinal cord are those which originate in area 4 of the frontal lobe and in the whole surface of the parietal lobe. The posterior division of area 4 (10) is the locus of origin for corticifugal systems terminating in the lateral nucleus of the thalamus, the red nucleus, the substantia nigra, the pons, the tegmentum of the subthalamus, midbrain and medulla oblongata, and in the spinal cord (frontospinal tract). The anterior division of area 4 (11, 12) sends corticifugal fibers to the lateral and medial nuclei of the thalamus, the substantia nigra, the pons, the tegmentum of the subthalamus, midbrain, and medulla oblongata, but *none to the nucleus ruber*. The corticifugal fibers from the parietal lobe (13) terminate in the dorsal thalamic nuclei, the pretectal region, the superior colliculus and the substantia nigra of the midbrain, the pons, and the spinal cord. The nerve fibers which reach the spinal cord pass via the pyramids and lie mainly in the inner zone of the lateral funiculus. None of the degenerating fibers from the parietal lobe were found terminating in any part of the tegmentum of the brain stem.

The pyramids themselves contain fibers having their origin in cell bodies not only of area 4 of the frontal lobe but also of the whole of the parietal lobe (13). Consequently, there is no locus in the spinal cord where it is possible to sever surgically any one of the known descending systems in pure culture. An attempt to assign function to a particular fiber system among the group severed in any particular monkey in this

series requires comparison of the sequelae of the operations performed in this and other spinal cord experiments. In addition, there must be a consideration of the results of damage to the corticifugal systems. Consideration of the latter systems is important for two reasons, (1) they have a direct bearing on the lesions produced here (the parietospinal and frontospinal were cut) and (2) the subcortical centers in which corticifugal systems terminate may be the foci from which descending spinal cord fibers originate.

In the macaque "spastic paralysis" follows removal of area 4. The selective incidence of this paralysis and that of the hypertonicity resembles the differential distribution of these two states in man (11, 14). Further, certain moities of the spastic state with minimal paralysis can be produced in this species by ablation of the anterior border of area 4 (15). On the other hand, hypotonic states can be produced. Removal of the parietal lobe (16) is followed by hypotonia without paralysis and surgical severance of the pyramids is followed by hypotonic paralysis (17). The selective incidence of the paralysis produced by interruption of the pyramids resembles that yielded by removal of area 4. Atrophy and abnormal "associated reactions" (5) follow both pyramidal sectioning and removal of area 4, but widespread contracture or muscle shortening results only from the latter procedure. The hypotonic paralysis resulting from surgical division of the pyramids can be modified in three ways. Removal of total area 4 or of the anterior border of area 4 superimposes upon the hypotonic paralysis the hypertonic state of hemiplegia (18). Extension of the pyramidal lesion to include either division of the neighboring tegmentum of the medulla oblongata (19) or damage to the adjoining pons area (20) produced hypertonic paralysis. Tower (20) found that lesions in the pons with only slight injury to the pyramids produced exaggerated postural and tendon reflexes, excessive tone of clasp-knife quality and readily elicitable clonus,—results which resemble those produced by removal of the anterior border of 4. Peele's (13) finding that the parietospinal fibers, which when interrupted by ablation of the parietal lobe results in a generalized hypotonia, pass through the pyramids to lie within the spinal cord either medial to the lateral frontospinal tract (cervical levels) or mingled with that tract (lower levels) suggests that the hypotonia of pyramidal section or that of deep lesions in the lateral funic-

ulus (21) may not be the result exclusively of section of the frontospinal tract itself, but rather of division either of the parietospinal fibers alone which travel with or near that tract, or of the combination of the parietospinal and the frontospinal systems.

It is plausible, therefore, to consider that the frontospinal tract controls the discreet component of phasic activity, that the parietospinal system maintains certain aspects of tone, and that some of the corticifugal fibers from area 4s to the tegmentum inhibit and control tone. The question that remains to be answered is what spinal cord fibers mediate this influence of 4s. Obviously they do not arise from 4s directly for ablation of that cortical area causes no degeneration in the spinal cord other than the extremely slight amount in the frontospinal tract. We will now consider the fiber groups possibly implementing the cortical inhibitory influences upon the skeletal muscle tone.

The results of surgical division of the descending systems made in this series of experiments were characterized in general by the dominance either of paralysis or of spasticity. Both the paralysis and the changes in tone showed several degrees of severity. The paralysis was directly proportional to the injury of the corticospinal tract (i.e., the frontospinal and parietospinal tracts). Extensive injury either in the lateral funiculus (W3L, W3L2) or surgical division of the pyramids (W7P, 510P) yielded severe paralysis, slight injury to the lateral funiculus (W8R, W9L, W5L) produced loss of initiation and of facility in use of the affected extremity, whereas negligible injury to the same area caused only loss of ease of initiation of movement and of strength in performance (W1R). The paralysis, whatever its degree, showed the selective distribution which characterizes all ablations of total area 4 in the macaque, for the retractors and adductors at the hip, the flexors of the knee, the dorsiflexors of the ankle and toes, and the evertors of the ankle were more paralyzed than their antagonists. Although the degree of paralysis varied with the number of corticospinal fibers severed, the large proximal muscles used in posture and progression were least paretic. No localization within this tract can account for this differential distribution, because the results were similar whether the whole tract was cut or whether the more dorsolateral division (W9L) or the more ventrolateral part (W5L) were injured.

Electrical stimulation of the surface of area 4 in this species (22)

showed that the area which yielded contraction of distal muscles was greater than that which produced contraction of proximal muscles. This fact suggested that the number of corticifugal fibers for the former musculature was greater than that for the latter and therefore might account for the greater paresis in the distal group. No such relationship, however, can be evoked to explain the differential distribution of paralysis among the large proximal muscles, for the retractors at the hip were as paralyzed as the muscles of the digits.

The tone of the striated musculature of the affected extremity evaluated by palpation and by resistance to passive movement was either unchanged, decreased, or increased. Increased tone was distributed in two general patterns; 1) the selective incidence characteristic of ablations of the anterior border of area 4 (4s) or of the whole of area 4, and 2) a distribution which can be interpreted at the present as peculiar only of the spinal cord lesion itself. Decreased tone followed the surgical division of the pyramids and three varieties of spinal cord lesions (W3L, W1R, W3L2).

The increased tone of the typical spastic state of cortical origin in the macaque is found in the protractors, internal rotators, and adductors at the hip, the extensors of the knee, the ventriflexors and invertors of the ankle. This distribution was found in W8R and W5L and was superimposed upon the pyramidal lesions in W7PC (except for the extensors of the knee) and 510PC. Consequently, the tone of the typical spastic state was produced, 1) with no real paralysis and 2) imposed upon a severe paralysis which had been hypotonic. The lesion in the lateral funiculus of the spinal cord in W8R and in 510PC interrupted similar extrapyramidal descending systems (reticulospinal and rubrospinal tracts) and similar ascending systems, the dorsal spinocerebellar tracts. In W5L and W7PC the lesion added two ascending systems, the ventral spinocerebellar and the lateral spinothalamic tracts, while in W7PC, the ventral funiculus was also injured including the vestibulospinal and possibly the ventral reticulospinal fibers. The common denominator spreads over the lateral reticulospinal tract, the rubrospinal tract, and the dorsal spinocerebellar system. The interruption of the latter alone (experiments not reported here) produced a marked hypotonia without paralysis. Tower (20) as noted above, produced the hypertonia of the spastic state by lesions in the pons

and only slight injury to the pyramids, without damage to the rubrospinal system. Further, there is no corticorubral system from area 4s. Therefore, it is logical to postulate that the interruption of reticulospinal fibers is followed by the appearance of the phenomena of release (1). The recent work of Mettler (6) does not rule out this interpretation.[5]

[5] Mettler (6) states that abnormal plantar and patellar reflexes may be produced without evidence of paralysis by "damage to the mesencephalic tegmentum (which usually produces a homolateral effect) or in the pons or medulla, damage to the area occupied by the rubrospinal system (which produces a homolateral effect)". He states further "There was no conclusive evidence that . . . abnormally overactive patellar reflexes can be evoked by reticulo-spinal or vestibulo-spinal system damage". Such a statement appears to argue against the conclusions to be drawn here. However, "overactive" reflexes were observed after cerebellar decortication (Rhesus J13M). Another animal showed quite selective damage of the decussation of the rubrospinal tracts (Papio J25M) and although one patellar reflex had a lowered threshold the response was of increased amplitude. Another animal (Rhesus J69M) cited as an example that the rubrospinal tract damage causes an "overactive" reflex showed a very loose patellar response of increased amplitude. Also, this same animal showed no damage to the efferent rubrospinal fibers of the left red nucleus yet the right patellar response not only had a lowered threshold but a response less loose and of less amplitude than the opposite. It is apparent that the term "overactive" as used by Mettler is not synonymous with the type of reflex described here as a brisk response with a lowered threshold. By the same reasoning Mettler's "overactive" reflex is not similar to the type of reflex seen following motor cortex lesions. Although the lowered threshold of tendon reflexes following discrete lesions in the lateral funiculus may indeed be due, partially at least, to rubrospinal tract damage the type of response (W5L) suggests that the interruption of other fibers (lateral reticulospinal) contribute to the "spastic" quality observed.

Mettler does not report any consistent and marked change in tone or resistance to passive movement following isolated rubrospinal tract damage. This is additional evidence that consideration of the lateral and ventral funiculus fibers severed in this experiment must include those whose origin is other than that of the red nuclei. Furthermore, as is shown by one of Mettler's monkeys (Rhesus J2) very low threshold reflexes with irradiation may be caused by tegmental damage not assiciated with any rubrospinal tract degeneration. This raises the question of the degree of effect that tegmental damage may have had on the reflexes in other animals of Mettler's series. In some of the animals (Rhesus Jp, Rhesus J5, Rhesus J69M) the patellar reflexes exhibited low threshold or were "greater and exaggerated". In these same animals no mention of reticulospinal tract damage is mentioned yet the medial lemniscus was damaged in two and the medial longitudinal fasciculus in the third. Both of these pathways contain reticulospinal fibers according to the same article (p. 72). Lastly, it is conceivable that such

The distribution of increased tone, which was not typical of the "spastic" state following ablation of total area 4 cannot be attributed to the interruption of any one tract. Although W1R and W9L shared a marked increase in tone in the adductors at the hip, the state of tone in the remaining muscles of the lower extremity was dissimilar. In W9L the cutting of the ventral spinocerebellar tract appeared to neutralize the effect of interruption of the lateral reticular system, for tone in the other muscles of the leg was almost normal. In W1R the definite decrease in tone cannot be assigned to one particular system, for not only were both spinocerebellar tracts severed, but also the parietospinal and the vestibulospinal. On the other hand, tone in the muscles of the left lower extremity of W1L was only slightly hypertonic. However, the slight increase in tone did not follow the pattern characteristic of area 4 ablations and was not commensurate with either the clonus or the state of the tendon reflexes (low threshold and brisk response of brief duration). It is possible that a certain neutralization of effect upon tone was produced by cutting both the vestibulospinal (23) and the reticulospinal tracts.

A generalized distribution of decreased tone characterized the two pyramidal animals and two of the spinal cord preparations (W3L, W3L2). In all four the frontospinal and the parietospinal fibers were completely severed. These preparations suffered from a hypotonic paralysis (the adductors at the hip, however, were hypertonic in the pyramidal preparations). The frontospinal and parietospinal fibers were severed either in the pyramids or in the spinal cord. Since removal of the parietal lobe (16) is followed by hypotonia without paralysis, it seems logical to consider that the decrease in resistance to passive movement shown by these preparations may be the result of division of the parietospinal fibers rather than that of the frontospinal tract itself. There is no obvious explanation of the difference in the condition of tone in the adductors in these two types of preparations. The interruption of a large part of the dorsal spinocerebellar tract might account for the decreased tone of the adductors in the spinal cord preparations. However, the intactness of this tract in the pyramidal

tegmental damage, associated with lesions of the red nuclei, may have a most important influence on the reflexes even though degenerating spinal cord fibers from such areas were not identified.

preparations cannot explain the individual selective incidence of increased tone in this muscle group, for the dorsal spinocerebellar fibers were subsequently cut in the pyramidal animals and the hypertonicity of the adductors remained.

Cannon, Beaton, and Ranson (21) produced hypotonic paresis with pendular reflexes of increased threshold by lesions in large part in the lateral funiculus. Although interruption of the lateral reticulospinal tract undoubtedly occurred in six of their animals and perhaps in two more, and although in two of their preparations, the ventral reticulospinal tract was probably involved, no evidence of spasticity was reported. These findings are not incompatible with those of this series. The incisions were so deep and extensive that many other tracts besides the reticulospinal ones were interrupted, namely:—the frontospinal, the rubrospinal, the parietospinal, and, in some instances, the vestibulospinal. It is apparent that interruption of these systems disguises the results of simultaneous damage to reticulospinal fibers (see results in W3L2).

The condition of the myotatic reflexes and the presence of tremor or of clonus did not vary directly with change in tone. Brisk and irradiating tendon reflexes and tremor were observed in two spinal cord preparations (W8R, W5L). The distribution of increased resistance to passive movement of the clasp-knife type in these macaques was that which characterized ablations of the anterior border of area 4 or of total area 4. No tremor or clonus was produced by the spinal cord lesions which transformed the hypotonic paralysis of the pyramidal preparations to hypertonia. Typical clonus was observed in only one macaque in this study (W1L). In this animal the brisk irradiating tendon reflexes accompanied a minimal increase in tone in a few muscles. Tremor was found only in those spinal cord preparations (W8R, W5L) in which tone was increased and the tendon reflexes were brisk and irradiating. Even in the spinal cord preparations tremor did not invariably accompany the brisk and irradiating tendon reflexes (W9L).

Different states of tone exist with hyperactive reflexes during certain stages in development of the infant macaque (24). Mann (25) demonstrated clinically that hyperactive reflexes do not vary directly with different degrees of tone following lesions in the central nervous system

of man. In this experiment hypotonicity or hypertonicity was accompanied by hyperactive tendon reflexes, but no instance of hypertonicity and hypoactive reflexes was observed. These findings suggest a simple quantitative difference in the lesions of nerve fibers mediating inhibitory influences. Thus, it might be considered that where a few such fibers are severed the first evidence of release appears in the tendon reflexes. As more such fibers are interrupted by lesions that do not interrupt many other fibers of opposing function the excitation of the peripheral mechanism is so easily elicited that the hypertonic state is evident as increased resistance to passive movement. This concept is supported by the finding that tendon reflexes remain brisk long after all signs of increased resistance to passive movement has disappeared in the young macaque (24).

Cutting the ventral funiculus in the adult macaque severs two theoretically opposing groups of fibers, the vestibulospinal and the reticulospinal. It is just possible as mentioned above that division of the former neutralizes the results of division of the latter. Damage to the vestibular nuclei in the cat decreases muscle tone (23). Similarly ventral and ventrolateral chordotomy (26) in clinical cases of extensor spasticity is followed by diminution of tone in the quadriceps femoris muscle without marked permanent effect on tendon reflexes or clonus. Therefore, an explanation of the appearance of brisk tendon reflexes and clonus without marked increase in tone could be assigned to the effect of minimal severance of inhibitory fibers or to the counteraction of division of the vestibulospinal system. Obviously the pathways mediating inhibitory influences were already interrupted in these cases, for they were spastic. Consequently severing a pathway which ordinarily mediates these influences (reticulospinal) will contribute nothing to the spastic state present. But simultaneous severance of the vestibulospinal tract would theoretically tend to decrease tone. Putnam (27) has treated cases of athetosis by cutting the ventral portion of the lateral funiculus; thus interrupting the vestibulospinal, reticulospinal, tectospinal, and possibly ventral corticospinal fibers. Subsequent to the operations there was no striking change in the myotatic reflexes. However, "hyperactive" reflexes, clonus, or Babinski's sign was present in about one half of the cases prior to operation. Furthermore, he states "when some deficit in the pyramidal tract co-

exists the knee jerk may acquire a rapid pendulous character". The pendulous quality of the reflexes of pyramidal monkeys usually become more "rapid", i.e. of lowered threshold and of more brisk response after spinal cord interruption of the reticulospinal fibers. However, to draw any conclusions as to the effect on muscle tone by the interruption of reticulospinal fibers in man from such cases is obviously difficult for two reasons. First, such severe central nervous system damage existed prior to the operations that some degree of effect might be masked. Second, the differentiation between true "spasticity" and the tenseness from attempting to control spasmodic movements is technically difficult.

Associated movements (Walshe's associated reactions) (28, 5), both tonic and phasic, were observed to be exaggerated in the extremities opposite the divided pyramids and in the lower extremity ipsilateral to spinal cord damage of the corticospinal fibers (W3L). These exaggerated associated movements disappeared when a lesion in the lateral funiculus (510PC) and one in the ventral and lateral funiculi (W7PC) were superimposed upon the previous division of a pyramid. Moreover, macaques in which many extrapyramidal fibers were initially damaged showed no exaggeration of associated movements. Rather, they were diminished. However, exaggeration of associated reactions is not a hall mark of pyramidal lesions. Mettler (29) observed that caudate and/or putamen lesions plus removal of the cortex caused a more notable tendency to perform associated reactions than did hemidecortication alone. The Vogts (30) considered associated movements a primary sign of disease of the striatum. However, removal of the pallidum impairs the ability to perform associated movements (29). Furthermore, cases of severe Parkinsonism show few if any of the common associated activities for they are apparently lost or obscured by the other changes. The present observations permit little clarification of the spinal cord pathways of these intricate influences in the Primates. It appears that a diminution or cessation of associated movements follow extrapyramidal lesions in the spinal cord of the macaque. Exaggeration of them following a spinal cord lesion depends on the intactness of the extrapyramidal fibers in the presence of a damaged pyramidal system.

This conclusion is particularly interesting because the removal of

the parietal lobe increases both the variety and the degree of associated movements resulting from a previous ablation of area 4 (11). This state of exaggerated associated reactions resembles that produced by surgical division of the pyramids. Furthermore, Peele (16) observed that associated reactions followed ablation of areas 3, 1, 2, and 5 of the parietal lobe (Kennard and Kessler, (31), reported none after removal of the total lobe). Since the parietospinal system must be considered to be one of the components of the pyramids (13), it is logical to believe that the increase in variety and degree of associated reactions which follows section of the pyramids as compared to their state after removal of area 4 reflects the physiological effect of this particular moiety of the pyramidal group. These experimental cortical ablations leave the extrapyramidal fiber groups of the spinal cord intact. Thus, the results of both cortical ablations and spinal cord lesions show it is necessary that the extrapyramidal fibers remain intact for exaggerated associated movements to appear.

Contracture as used in this study means the shortening of the length to which a muscle can be stretched either passively or by the contraction of its antagonist. Prior to this study contracture was not reported as one of the sequelae of division of a pyramid in any macaque operated on past infancy (32). Both pyramidal preparations in this series, however, showed slight contractures of the adductors at the hip, and of the ventriflexors of the foot and toes. The contractures which followed interruption of extrapyramidal fibers in the spinal cord in the monkeys of this study were more severe than any reported as sequelae of cortical lesions, except those which followed bilateral removal of the frontal lobe (11). The ablation of the parietal lobe is not followed by contracture (16). However the addition of removal of the parietal lobe to that of area 4 increases the severity of the contracture which resulted from removal of area 4 (11). The most severe contractures seen in the macaque followed complete removal of the telencephalon (33). Some quantitative factor seems to be at work, so that the greater the loss of extrapyramidal systems, the greater the contracture. The effectiveness of a relatively small spinal cord lesion in causing severe contractures may depend on the structural compactness of the descending axis cylinders within it.

Why certain muscles and muscle groups should be more contractured

than others remains an intriguing question, and one not to be answered with information now available (11). In general the muscles innervated by motor cells lying in the more central part of the ventral horn (34, 35) were the ones most involved. Also, these same muscles were the ones maintained in the least stretched or lengthened state by the more common postural attitudes assumed during convalescence. However, this relationship between posture and contracture is obviously not the only factor (if it is one) governing muscle shortening for the same muscle groups in some of these animals did not show contracture. Although Tower (17) has suggested that contractures result from overactivity, this state of muscle shortening was found in a few muscles of the pyramidal preparations and in hypotonic as well as in hypertonic muscles of the spinal cord preparations. Furthermore, not all hypertonic muscles showed shortening. These observations stimulate one to seek further for the etiology of contracture.

Atrophy of skeletal muscle followed not only surgical division of the pyramids but also interruption of extrapyramidal pathways in the spinal cord. The former operation effected a greater wasting of distal musculature, the latter, of proximal musculature. Following pyramidal lesions the greater wasting was found in the distal musculature but following isolated extrapyramidal lesions of the spinal cord wasting was most marked in the proximal muscles. The atrophy of the latter may have resulted from the obvious reluctance of these animals to initiate movement with the affected appendage. Limitations in the use of the word "atrophy" have been pointed out.

Four "superficial" reflexes were studied. Severe injury to the corticospinal tracts either at the pyramidal level or in the lateral funiculus was followed by loss of the abdominal reflex and of the cremasteric reflex. The brisk adduction of the hallux (associated usually with flexion) which normally follows pinching of the middle toe was absent in the pyramidal preparations and in the macaque with the complete division of the lateral and ventral funiculi (W3L2). In those in which the extrapyramidal fibers were more damaged than the pyramidal fibers the adduction of the hallux was quicker than found in the normal monkey. The plantar reflex appeared to be inconsistent. Extension and fanning of the toes was not observed to be a sign of pyramidal damage. Rather, this form of response to a moving stimulus on the

lateral border of the plantar surface was found in instances of minor damage to the lateral or the ventral funiculus and in instances of severe damage to both. Indeed, in one macaque in which the corticospinal tract was most discretely injured (W3L) the response was flexion of the toes.

These results of change in the plantar reflex resemble in part those reported in the study of Fulton and Keller (36). They observed that a low semisection of the spinal cord in monkeys produced a definite Babinski reflex on the side of the lesion. Neither removal of the cortical leg area nor complete removal of one cerebral hemisphere and the underlying thalamus and striatum was followed by such a response.[6] The observations reported in this study do not warrant their conclusion that complete freedom from control of higher centers is the prerequisite for the appearance of extension and fanning of the toes. However, the present findings and those of Fulton and Keller indicate that in the lower primate this pathological response results from release of the spinal cord reflex area from higher centers, some of which may lie in the midbrain or medulla.

In conclusion the descending pathways within the spinal cord of the Macaca mulatta fall into two main groups; those involved directly in the execution of fine purposive, discrete movements, and those maintaining a highly modifiable state of tone or fixation of the muscles whereby the discrete movements are more easily performed. The former group was demonstrated once again to be the frontospinal group of the corticospinal. The latter group comprise several types of fibers, parietospinal, rubrospinal and vestibulospinal and reticulospinal. Interruption of the parietospinal (11) fibers at the cortical level gives hypotonicity without paralysis and interruption of the same moiety by pyramidal sectioning or by a discrete lesion in the lateral funiculus of the spinal cord (W3L) where their interruption includes also that of the frontospinal fibers again produces predominantly hypotonic paralysis. The reticulospinal fibers damaged in the lateral funiculus with minimal injury to the corticospinal produces the phenomena of release, namely, brisk, irradiating tendon reflexes, tremor and resistance to passive movement of the clasp-knife type having a distribution typical of

[6] The latter operation in one animal produced plantar extension on stimulation of the skin over the ankle.

cortical ablation of area 4s or of total area 4. Removal of 4s and the underlying caudate or putamen nuclear material apparently exaggerates the symptoms characteristic of ablation of 4s only (37). This fact and the intimate relation of the striatum, nigra and tegmental nuclei of the midbrain (38) suggest corticotegmental fibers may not be the only pathway of inhibitory influences mediated eventually by the reticulospinal fibers. Interruption simultaneously of the ventral reticulospinal and vestibulospinal fibers resulted in brisk hyperactive reflexes and only slight increase in tone. As has been mentioned this evidence of only slight release may be due to the interruption of fibers having in a sense antagonistic or equalizing influences.

The extrapyramidal systems seem to set a stage on which the pyramidal system acts. The extrapyramidal system exerts in part an inhibiting influence, holding in abeyance reflex activities of lower motor neurone circuits. In the present study the withdrawal of this effect becomes most obvious in the antigravity muscles. Damage to these fibers is reflected in reluctance to use the affected extremity. When movement is finally initiated, however, its performance is excellent. Just as the corticospinal fibers are more intimately associated with the more distal muscles and concerned mainly with discrete and fine movements so the extrapyramidal fibers, especially the reticulospinal system, seem more closely associated with proximal muscles. Not only are these proximal muscle groups important in posture and progression but also in the fixation of the extremity which accompanies initiation and execution of refined phasic activity. The destruction of the corticospinal system results in difficulty in skilled performance and in an atrophy predominantly of distal muscles and that of the reticulospinal in reluctance to fix the extremity for voluntary movement and in an atrophy predominantly of proximal muscles.

Electrical stimulations of extrapyramidal cortical areas of the monkey (39) cause movements that may be simple or complex synergies. Such movements may be elicited from widely separated foci. They are sustained and climactic; elaborating progressively into more complex movement. Apparently these various extrapyramidal centers share final common pools of neurones. Stimulation of them sets off an "avalanche" of impulses in many neurones resulting in a generalized effect.

Although it is impossible to apply without qualifications the results

of this study to man, nevertheless it is interesting to note that the anatomical separation of spasticity and paralysis found in differential lesions of the spinal cord of the macaque has its counterpart in clinical reports. Bergmark (40) described a few cases of paralysis of cortical origin unaccompanied by spasticity and reported a case (# 23) of monoplegia in which the finer motility of the hand returned but the tendon reflexes remained brisk in the distal joints of the arm. Spielmeyer (41), Bielschowsky (42) and Finkelnburg (43) reported spasticity in the presence of an anatomically intact pyramidal tract. Lassek (44) has reported a large series of autopsies on individuals with histories of having had one or more of the clinical signs usually associated with the spastic state. Only 17 (14.3%) showed histological evidence of damage to the pyramidal tract. Evidence (45, 46) now indicates that spastic paralysis is due to the interruption of more than the corticospinal system. The results of this study suggest that the anterior division of area 4, the midbrain tegmentum and the reticulospinal tracts may be the route of the "spasticity" component of spastic hemiplegia. Semi-section of the spinal cord in man results in spasticity (47, 48) but such a lesion in the macaque is followed by hypotonicity (36). This difference may reflect an even greater importance of the reticulospinal system in the human than in the monkey.

Conclusions

The results of this study show that the facets of spasticity unassociated with paralysis can be produced by lesions in the spinal cord of the Macaca mulatta. The interruption of the reticulospinal fibers seems to produce this group of symptoms. It is apparent that there is an intimate functional and anatomical relation between the corticifugal systems from area 4s and the reticulospinal tracts. The division of other spinal cord systems (such as parietospinal, rubrospinal, vestibulospinal, and spinocerebellar) in conjunction with the reticulospinal fibers prevents the appearance of spasticity. That their interruption by hemisection of the cord does not prevent the appearance of spasticity in man may signify an even greater importance of the reticulospinal system in the human than in the macaque.

Brisk tendon reflexes of low threshold were associated either with hypotonicity or with hypertonicity of the same muscles. The latter state of tone was always found with brisk tendon reflexes of low

threshold. Interruption of the pyramidal tract severs fibers of multiple cortical origin and results in 1) impairment of phasic activity, 2) hypotonia of some muscles, and 3) definite evidence of release. No pattern of anatomical segregation of corticospinal fibers (i.e., frontospinal and parietospinal) was found in the lateral funiculus.

As a general rule the effectiveness of the function of a muscle made paretic by a central nervous lesion increases progressively with the number of other muscles employed simultaneously and coordinately.

Associated movements of an extremity depend on the integrity of the extrapyramidal fibers in the spinal cord. Their exaggeration follows isolated pyramidal tract damage.

Atrophy of the proximal muscles is most marked following extrapyramidal lesions, that of distal musculature following pyramidal lesions.

Although a slight degree of contracture results from pyramidal lesions, it is more intimately and extensively associated with extrapyramidal damage. Contracture occurs in both hypotonic and hypertonic muscles.

An increased briskness of adduction of the hallux on pinching the middle toe is the most reliable superficial reflex for the presence of isolated damage to the extrapyramidal fibers in the spinal cord.

Spastic paralysis follows division of two anatomically discrete systems. The paralysis appears after a lesion of the frontospinal tract (older usuage, the corticospinal); the spasticity after interruption of extrapyramidal fibers, probably the 4s-tegmentum fibers and/or the reticulospinal system.

I thank Dr. Marion Hines, whose generosity of ideas and whose thoughtful and continuous assistance and patience made this work a pleasure.

BIBLIOGRAPHY

1. Jackson, J. H.: Selected Writings, ed. by J. Taylor, London, 1932, **2**, pp. 510.
2. Gowers, W. R.: A Manual of Diseases of the Nervous System, P. Blakiston's Son and Co., Philadelphia, 1899.
3. Dejerine, J.: Semiologie des Affections du Systeme Nerveaux, Masson et Cie, Paris, 1926.
4. Oppenheim, H.: Text-Book of Nervous Diseases for Physicians and Students, T. N. Foulis, London, 1911.
5. Walshe, F. M. R.: Physiological analysis of some clinically observed disorders of movement, Lancet, 1929, **1**, 963.

6. METTLER, F. A.: Physiologic consequences and anatomic degenerations following lesions of the primate brain-stem: Plantar and patellar reflexes, J. Comp. Neurol., 1944, **80,** 69.
7. TOWER, S. S.: Private communication.
8. RADEMAKER, G. G. J.: Das Stehen, Julius Springer, Berlin, 1931.
9. BARD, P.: Studies on the cortical representation of somatic sensibility, Harvey Lectures, 1937–38.
10. LEVIN, P. M.: The efferent fibers of the frontal lobe of the monkey (Macaca mulatta), J. Comp. Neurol., 1936, **63,** 369.
11. HINES, MARION: Control of movements by the cerebral cortex in primates, Biol. Rev., 1943, **18,** 1.
12. VERHAART, W. J. C. AND KENNARD, M. A.: Corticofugal degeneration following thermocoagulation of areas, 4, 6, and 4-s in Macaca mulatta, J. Anat., 1940, **74,** 239.
13. PEELE, T. L.: Cytoarchitecture of individual parietal areas in the monkey (Macaca mulatta) and the distribution of the efferent fibers, J. Comp. Neurol., 1942, **77,** 693.
14. HINES, MARION: Significance of the precentral motor cortex. The Precentral Motor Cortex, ed. by Paul C. Bucy, Urbana, 1944, Ch. 17, 461.
15. HINES, MARION: The "motor" cortex, Bull. Johns Hopkins Hosp., 1937, **60,** 313.
16. PEELE, T. L.: Acute and chronic parietal lobe ablations in monkeys, J. Neurophysiol., 1944, **7,** 269.
17. TOWER, S. S.: Pyramidal lesion in the monkey, Brain, 1940, **63,** 36.
18. TOWER, S. S. AND HINES, MARION: quoted by Tower, S. S. (ref. 32).
19. TOWER, S. S.: Private communication.
20. TOWER, S. S.: The production of spasticity in monkeys by lesions in the pons, Anat. Rec., 1942, **82** (Suppl.), 450.
21. CANNON, B. W., BEATON, L. E., AND RANSON, S. W.: Nature of paresis following lateral cortico-spinal section in monkeys, J. Neurophysiol., 1943, **6,** 425.
22. HINES, MARION AND BOYNTON, E. P.: The maturation of "excitability" in the precentral gyrus of the young monkey (Macaca mulatta), Contrib. Embryol. Carnegie Inst., 1940, **28,** 309.
23. FULTON, J. F., LIDDELL, E. G. T., AND RIOCH, D. MCK.: The influence of unilateral destruction of the vestibular nuclei upon posture and the knee-jerk, Brain, 1930, **53,** 327.
24. HINES, MARION: The development and regression of reflexes, postures, and progression in the young macaque, Contrib. Embryol. Carnegie Inst., 1942, **30,** 154.
25. MANN, L.: Ueber das Verhalten der Sehnenreflexe und der passiven Beweglichkeit bei der Hemiplegie, Mschr. Psychiat. Neurol. 1897, **1,** 409.
26. HYNDMAN, O. R.: Physiology of the Spinal Cord. The influence of chordotomy on existing motor disturbances, J. Nerv. Ment. Dis., 1943, **98,** 343.

27. PUTNAM, T. J.: Results of treatment of athetosis by section of extrapyramidal tracts in the spinal cord, Arch. Neur. and Psychiat., 1938, **39,** 258.
28. WALSH, F. M. R.: On certain tonic or postural reflexes in hemiplegia, Brain, 1923, **46,** 1.
29. METTLER, F. A.: Extensive unilateral cerebral removals in the primate: Physiologic effects and resultant degeneration, J. Comp. Neurol., 1943, **79,** 185.
30. VOGT, C. AND VOGT, O.: Zur Lehre der Erkrankungen des striaren Systems, J. Psychol. Neurol. Lpz., 1920, **25,** 627.
31. KENNARD, M. A. AND KESSLER, M. M.: Studies of motor performance after parietal ablations in monkeys, J. Neurophysiol., 1940, **3,** 248.
32. TOWER, S. S.: The pyradmidal tract. The Precentral Motor Cortex, ed. by Paul C. Bucy, Urbana, 1944, Ch. 6, 149.
33. WOOLSEY, CLINTON: Private communication.
34. BOK, S. T.: Strukturlehre des Ruckenmarkes. Handbuch der mikrokopischen Anatomie des Menschen, von Mollendorff, Berlin, 1928, **4,** 502.
35. BIKELES, G.: Sur Lokalization im Ruckenmark, Dtsch. Nervenheilk., 1905, **29,** 180.
36. FULTON, J. F. AND KELLER, A. D.: The Sign of Babinski. A study of the evolution of cortical dominance in primates, Charles C. Thomas, Springfield, Ill., 1932.
37. KENNARD, M. A. AND FULTON, J. F.: Corticostriatal interrelations in monkey and chimpanzee, Res. Publ., Ass. nerv. ment. Dis., 1942, **21,** 228.
38. PAPEZ, J. W.: A summary of fiber connections of the basal ganglia with each other, Res. Publ. Ass. nerv. ment. Dis., 1942, **21,** 21.
39. TOWER, S. S. AND HINES, MARION: Quoted by Hines, Marion (ref. 11).
40. BERGMARK, G.: Cerebral monoplegie, with special reference to sensation and to spastic phenomena, Brain, 1909, **32,** 342.
41. SPIELMEYER, W.: Hemiplegie bei intakter Pyramidenbahn (Intrakorticale Hemiplegie), Munch. Med. Wchnschr., 1906, **53,** 1404.
42. BIELSCHOWSKY, M.: Iber Hemiplegie bei intakter Pyramidenbahn. J. f. Psychol. u. Neurol., 1918, **22,** 225.
43. FINKELNBURG, R.: Partielle Rindenatrophie und intakte Pyramidenbahn in einen Fall von Kongenitaler spastischer Paraplegia, Dtsch. Zeitschrift. f. Nervenheilk., 1913, **46,** 163.
44. LASSEK, A. M.: The human pyramidal tract, Arch. Neur. and Psychiat., 1944, **51,** 213.
45. WALSHE, F. M. R.: On the genesis and physiological significance of spasticity and other disorders of motor innervation, with a consideration of the functional relationships of the pyramidal system, Brain, 1919, **42,** 1.
46. LUBIN, A. J.: Relationship and function of the pyramidal tract, Am. J. Med. Sci., 1945, **209,** 111.
47. GRINKER, R. R.: Neurology, Charles C. Thomas, Springfield, Ill., 1943.
48. FORD, F. R.: Diseases of the Nervous System in Infancy, Childhood, and Adolescence Charles C. Thomas, Springfield, Ill., 1945.

EXPLANATION OF ILLUSTRATIONS

The central figure in each plate represents the spinal cord lesion. The descriptions below present first the degeneration in the spinal cord above the lesion and lastly the degeneration occurring below the level of the lesion. At the bottom of Plate II is presented the degeneration on one side of the spinal cord following section of the opposite pyramid. In Plate III degeneration of the lateral corticospinal fibers is observed above the spinal cord lesion of 510PC and W7PC because the opposite pyramid had been sectioned previously in both animals. A key to the degenerated fibers is presented in Plate III.

PLATE I

W8R—Schematic diagrams showing degeneration at level Th.5 of dorsal and ventral spinocerebellar fibers; the lesion at Th.7; and degeneration at Th.10 of lateral corticospinal, lateral reticulospinal, and rubrospinal fibers.

W9L—Schematic diagrams showing degeneration at level Th.5 of dorsal spinocerebellar fibers; the lesion at Th.7; and degeneration at Th.11 of lateral corticospinal, lateral reticulospinal, and rubrospinal fibers.

W5L—Schematic diagrams showing degeneration at level Th.4 of dorsal and ventral spinocerebellar fibers; the lesion at Th.7; and degeneration at L.1 of lateral corticospinal, lateral reticulospinal, and rubrospinal fibers.

W1L—Schematic diagrams showing degeneration at level C.6 of ventral spinothalamic fibers; the lesion at Th.7; and degeneration at L.3 of ventral reticulospinal and vestibulospinal fibers.

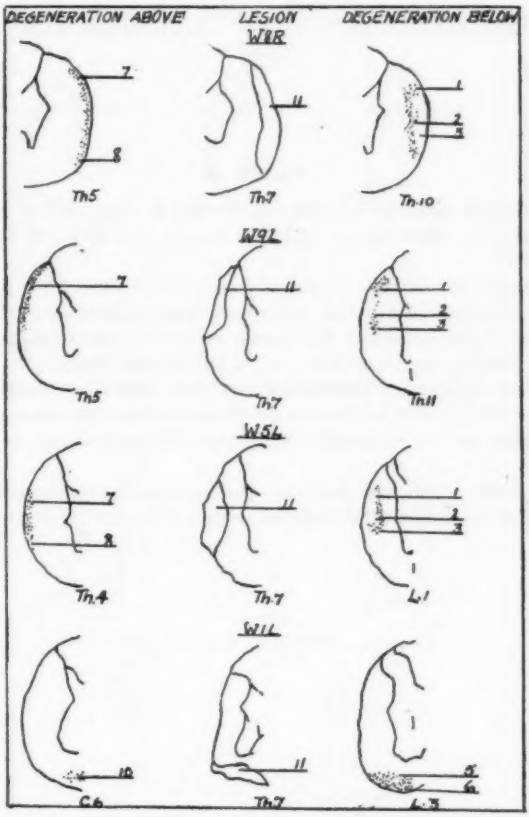

DEGENERATION ABOVE
LESION
DEGENERATION BELOW
W8R
7
8
Th5
11
Th7
1
2
3
Th10
W9L
7
Th5
11
Th7
1
2
3
1
Th11
W5L
7
8
Th4
11
Th7
1
2
3
1
L1
W11L
10
C6
11
Th7
1
5
6
L3

PLATE II

W3L—Schematic diagrams showing degeneration at level Th.2 of dorsal spinocerebellar fibers; the lesion at Th.7; and degeneration at L.3 of lateral corticospinal fibers.

W3L2—Schematic diagrams showing degeneration at level Th.3 of dorsal and ventral spinocerebellar, lateral and ventral spinothalamic fibers; the lesion at Th.6; and degeneration at L.2 of lateral and ventral corticospinal, lateral and ventral reticulospinal, rubrospinal, and vestibulospinal fibers.

W1R—Schematic diagrams showing degeneration at level C.6 of dorsal and ventral spinocerebellar, lateral and ventral spinothalamic fibers; the lesion at Th.7; and degeneration at L.3 of lateral and ventral corticospinal, and vestibulospinal fibers.

W7P and *510P*—Schematic diagrams showing degeneration respectively at S.1 and Th.5 of the corcicospinal fibers following sectioning of the opposite pyramid.

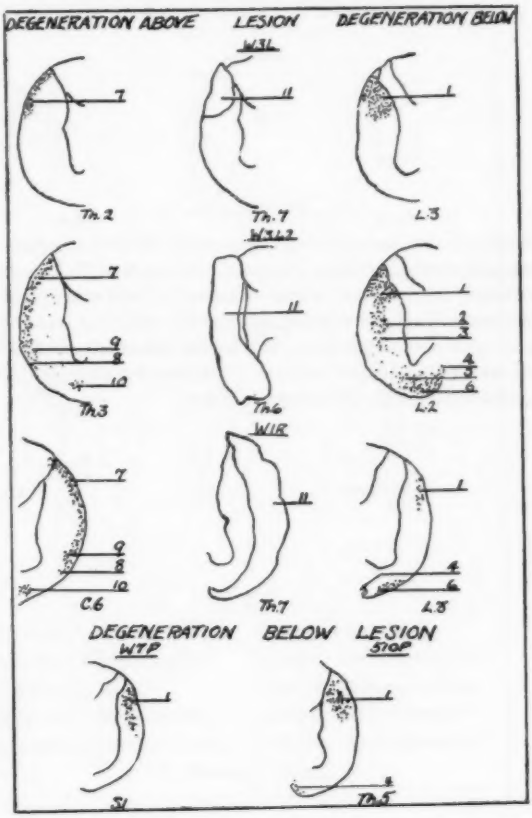
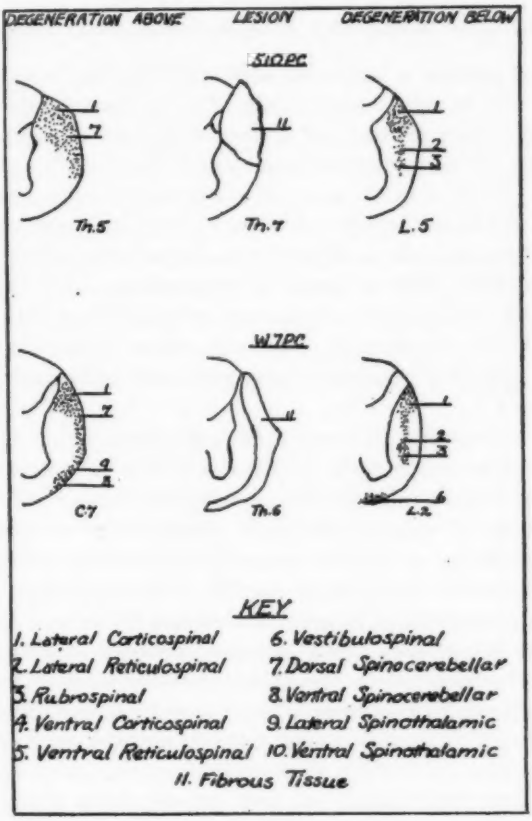

DEGENERATION ABOVE
LESION
DEGENERATION BELOW
W3L
7
11
1
Th.2
Th.7
L3
W3L2
7
11
1
2
3
9
8
4
5
10
6
Th3
Th6
L2
W1R
7
11
1
9
8
4
6
10
C6
Th7
L3
DEGENERATION BELOW LESION
WTP
STOP
1
1
S1
Th5

PLATE III

510PC—Schematic diagrams showing degeneration at Th.5 of lateral corticospinal and dorsal spinocerebellar fibers; the spinal cord lesion at Th.7; and degeneration at L.5 of lateral corticospinal, lateral reticulospinal and rubrospinal fibers.

W7PC—Schematic diagrams showing degeneration at C.7 of lateral corticospinal, dorsal and ventral spinocerebellar, and lateral spinothalamic fibers; the spinal cord lesion at Th.6; and degeneration at L.2 of lateral corticospinal, lateral reticulospinal, rubrospinal, and vestibulospinal fibers.


DEGENERATION ABOVE
LESION
DEGENERATION BELOW
S10PC
Th.5
Th.7
L.5
W7PC
C7
Th.6
L.2
KEY
1. Lateral Corticospinal
2. Lateral Reticulospinal
3. Rubrospinal
4. Ventral Corticospinal
5. Ventral Reticulospinal
6. Vestibulospinal
7. Dorsal Spinocerebellar
8. Ventral Spinocerebellar
9. Lateral Spinothalamic
10. Ventral Spinothalamic
11. Fibrous Tissue

TWO CASES OF PERIARTERITIS NODOSA OCCURRING IN THE FIRST MONTH OF LIFE

HARRY A. WILMER, PH.D., M.D.[1]

From the Department of Pathology, The Johns Hopkins Medical School

Two cases of periarteritis nodosa discovered at autopsy are reported in this communication. The clinical symptoms of the first case were manifest in the fourth week of life, and the patient died in the fifth week. The second infant came to necropsy at ten days of age. I have been able to find in the literature records of only two other cases occurring in the first year of life. Krzyszkowski (1) discovered a case of periarteritis nodosa at autopsy in a two and one-half month old infant. This was reported in Poland in 1899. The second case was reported by Thinnes in Germany in 1924 (2) who described an autopsy of a nine month old child. Apparently the diagnosis of periarteritis nodosa has never been established clinically within the first year of life.

Rich (3, 4) reported eight adult cases of periarteritis nodosa all coming to autopsy within a relatively short period of time, each of whom had had a hypersensitive reaction to foreign serum or to sulfonamides shortly before death. Rich and Gregory (5) then produced typical diffuse periarteritis nodosa in rabbits by establishing a condition analagous to serum sickness in man, and showed that it was a manifestation of the anaphylactic type of hypersensitivity. Lesions characteristic of rheumatic carditis result from similar experiments (6). In view of the fact that this disease can be produced by a hypersensitive reaction to different types of sensitizing antigens, the appearance of two cases within the first month of life is of singular interest in relation to the nature and source of the inciting antigen. In one of the cases it seems possible that the lesions might have been produced *in utero*.

CASE I

Case History: M. W. (No. A-36673) was born June 25, 1944 on the Obstetrical Service of the Johns Hopkins Hospital. Physical

[1] National Research Council Fellow in the Medical Sciences.

examination at the time of birth and one week later revealed a normal, colored, female infant. No abnormalities were noted.

When the child was twenty five days old, July 20, 1944, she suffered from symptoms which her mother interpreted as abdominal pain, "puffiness" of the hands and feet, and vomiting. During the ensuing four days vomiting continued, especially following orange juice feedings. The mother observed a few "red blotches" on the face which she stated had been present intermittently from birth.

On July 25th the infant was seen in the Out-Patient Dispensary in the Department of Pediatrics. Examination at that time failed to reveal any petechiae or purpuric areas. Edema of the eyelids was noted, and the mother said that the eyelids had been "puffy" since birth. There was no fever. The infant was not breast fed, but had received cow's milk formula. She had been given orange juice since the first week of life, cod liver oil, and milk of magnesia or castor oil when constipated. Since the dispensary examination revealed nothing remarkable the child was sent home; her mother was advised to give vitamin C preparation in place of orange juice, and admonished against giving castor oil.

Four days later, July 29, 1944, petechiae appeared on the face, hands, arms, feet, and abdomen, and the temperature rose to 39°C. There were three loose green stools which did not contain blood. Twice this day and twice the next, the child vomited, and each time, according to the mother, brought up bright red blood; she was then brought to the emergency room of the dispensary.

Physical examination: The infant was admitted to the Harriet Lane Home for Invalid Children at the Johns Hopkins Hospital on July 30, 1944. Her development, hydration, and nutrition were good, and she did not seem acutely ill. Her temperature was 38.5°C., her weight 3200 Gm. compared with a birth weight of 3210 Gm. Edema of the eyelids was present. Petechiae and purpuric areas were noted on the face, extremities, abdomen and base of the nailbeds. These did not blanch on pressure. The skin was cool and mottled. It was thought that the throat was moderately inflamed. The conjunctivae were not injected; pupils were round and equal, reacted to light and accomodation. The heart and lungs were normal. Although the spleen could not be felt, the liver was palpable 4 cm.

below the costal margin. The lower margin of the right kidney was palpable and seemed to the examiner to be unusually prominent. There was no abdominal tenderness.

Laboratory: Hemoglobin 10 Gm.; red blood cells 3,000,000; white blood cells 21,000 with 67 per cent adult polymorphonuclear neutrophils, 6 per cent immature polymorphonuclears, and 27 per cent lymphocytes. No platelets were seen on the routine smears. The catheterized urine was amber, acid, contained neither sugar nor acetone, and the quantity was insufficient for specific gravity determination. The centrifuged sediment contained 0–5 red blood cells and 5–10 white blood cells per high power field. On July 30 blood cultures grew hemolytic staphylococcus aureus, but cultures on the following two days were negative. The non-protein nitrogen was 57 mgm. per cent. Throat culture was not made. Blood carbon dioxide combining power was 46 volumes per cent. Cerebrospinal fluid was sterile. Stool guaiac was positive. Serological tests for syphilis were negative. Blood level of sulfadiazine on July 31 was 7.2 mgm. per cent.

Course in hospital: Following admission the patient vomited twice on July 30, but there was no blood in the vomitus. The diarrhea ceased. Soon after admission the child was given 0.1 Gm. of sulfadiazine every four hours until July 31. Shortly after morning rounds on that day the infant had a right sided convulsion which is said to have consisted mostly of twitchings, and which lasted about 10 minutes. She was treated with 100 cc. of normal saline subcutaneously, and 8 mgm. of sodium luminal intravenously.

At this time septicemia or renal thrombosis was considered a likely diagnosis. Before further diagnostic procedures could be performed the child expired on the morning of August 1. This was 37 days after birth, 12 days after the onset of the first symptoms, but only 3 days after the beginning of the final clinical episode.

Family history: Careful inquiry into the family history revealed one other sibling who was healthy and did not suffer from asthma, eczema, angioneurotic edema or apparently any disease of hypersensitivity. There was no history of allergic disease in the father, or the father's or mother's families, but the mother had developed hives on a number of occasions during the past five years. These

did not appear in the winter, but occurred with greatest frequency in the summer. The only food to which she was known to be sensitive was tomatoes.

The mother's obstetrical history (No. 303765) states that she was free from allergic symptoms during pregnancy. Serological tests for syphilis were negative. Blood pressure, urine and hemoglobin determinations were normal. She did not receive serum or sulfonamide therapy during the period of hospitalization.

Autopsy: (No. 19067) The body is that of a female colored infant measuring 52 cm. crown-heel length, weighing 3500 Gm. There is no evidence of malnutrition. Several petechiae, a few centimeters in diameter, are seen in the skin of the extremities. The pulmonary artery is opened *in situ* and no thrombus or embolus is seen. The heart is normal. Bronchi contain copious amounts of frothy hemorrhagic fluid, and there are widespread areas of hemorrhagic consolidation in both lungs. The liver, gall bladder, pancreas, spleen, intestine and mesentery appear grossly normal.

The left adrenal weighs 3.5 Gm. and is normal in form, color, and consistency. The cortex, intermediate zone, and medulla can be clearly distinguished. An enormous mass in the region of the right adrenal is bound by thick fibrous tissue at the hilum of the right kidney which faces cephalad, so that the kidney lies in the transverse position (Fig. 1).

Both renal cortices are pale and swollen. The left kidney weighs 25 Gm. The right kidney together with the right adrenal mass weighs 85 Gm.; the adrenal mass measures 4 x 5.5 x 1.5 cm. The cut surface of the right adrenal reveals a brownish-grey capsule, 4 to 6 mm. in thickness. In the center is a cavity containing necrotic tissue and old blood.

The ureters, tubes, ovaries and vagina are normal. Lines of ossification of the ribs are straight and narrow. The bone marrow is pale. The brain is grossly normal.

Microscopic examination: Periarteritis nodosa is manifest in sections of the adrenals, heart, uterus (Fig. 2), kidney, liver, tongue, pancreas and intestine. The right adrenal mass is surrounded by a thin fibrous capsule; the central part is largely necrotic with areas of fresh hemorrhage, and bilirubin crystals. Cells of the adrenal cortex can be

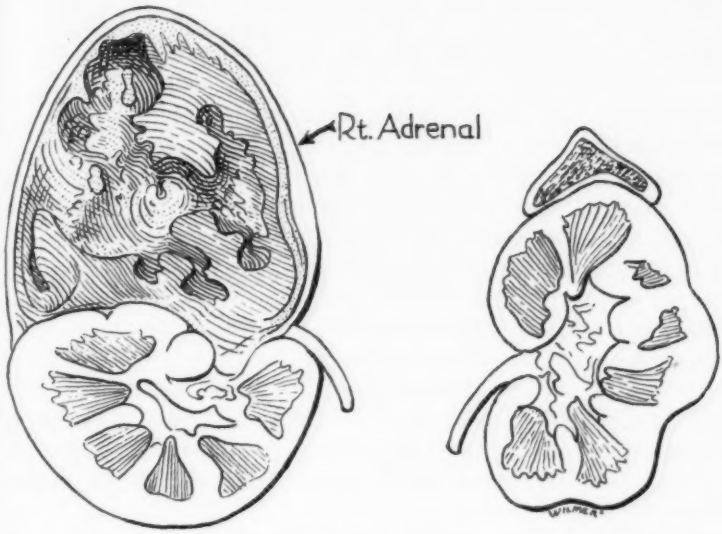


FIG. 1. DRAWING OF RIGHT AND LEFT KIDNEYS AND ADRENALS SHOWING ENORMOUS RIGHT ADRENAL WITH NECROTIC CENTER, AND THICK FIBROUS CAPSULE

Note transverse position of right kidney

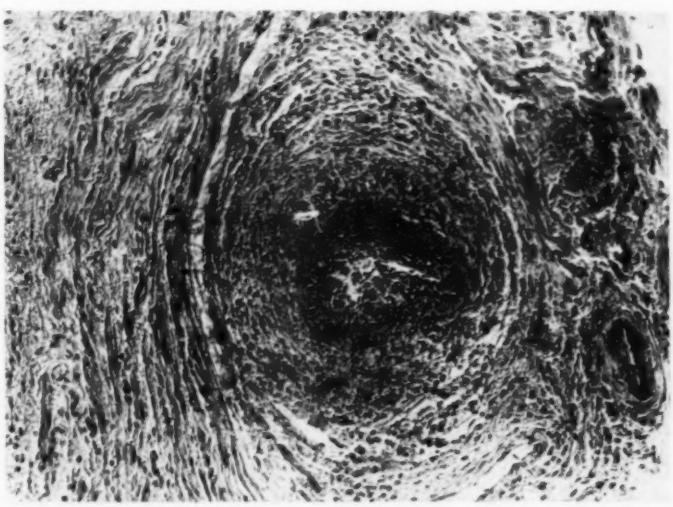


FIG. 2. PHOTOMICROGRAPH OF LESION OF PERIARTERITIS NODOSA FROM THE UTERUS OF CASE I (AUTOPSY 19067)

The perivascular infiltration of cells, necrotic media and intimal proliferation can be noted.

recognized in places at the periphery where they are still preserved. In the margins of the necrotic mass small abscess-like foci of polymorphonuclear neutrophil cells can be seen. Gram stains of the tissue show colonies of cocci, most of which stain red and probably represent dead bacteria, for among them are scattered gram positive cocci. Many small arteries in the capsule show characteristic lesions of periarteritis nodosa. Despite a careful search no thrombi are found in suprarenal arteries or veins. The left adrenal, with the exception of vascular lesions of periarteritis nodosa, is normal.

The vascular lesions show all degrees of the process. The media is often completely necrotic and smudgy or hyaline in appearance, and there is perivascular infiltration with mononuclear cells and eosinophilic leucocytes. There are more advanced lesions in which adventitial fibrosis is seen.

In the pulmonary alveoli there are scattered areas of hemorrhage and mononuclear infiltration. Hyaline membranes line some of the alveolar walls. There are no bacteria manifest in the special stains. The pathologic picture is somewhat similar to that of rheumatic pneumonitis (9). At the base of the mitral valve a small focus of necrotic collagen with surrounding mononuclear and polymorphonuclear cells is seen. In the kidney, in addition to the typical vascular lesions with occasional small thrombi, the glomeruli show an increase in cellular content with hyalin thrombi in glomerular capillaries and necrosis of some of the loops. Some of the tubules contain blood. The ovary, hypophysis, bladder and ribs are normal. A section taken through a small purpuric area in the skin reveals only ulceration and extravasation of red blood cells and occasional polymorphonuclear neutrophils into the corium. The brain is normal.

CASE II

Case history: C. S. (No. A-22419) was a 10 day old colored male infant admitted to the Harriet Lane Home for Invalid Children at the Johns Hopkins Hospital at 4 a.m. October 14, 1941; he expired at 7:25 p.m. the same day.

The infant weighed 8 pounds 2 ounces at birth and there was no cyanosis, hemorrhage, jaundice, or any other abnormality noted. Delivery was performed at home by the family physician. The child was breast fed, and nursed satisfactorily.

Two days before admission to the hospital the child vomited profusely in a projectile manner. The vomitus contained no blood. About two hours before admission the infant developed increasing respiratory difficulty. Dyspnea became severe, and when the child suddenly grew pale he was brought to the Harriet Lane Home. He had not vomited his last feeding given four hours previously, and bowel movements were normal.

Physical examination: Respirations were rapid and irregular, with two short, jerky excursions and one deep prolonged breath. Percussion notes were dull anteriorly and posteriorly except over the right base. On auscultation, breath sounds were decreased while numerous moist râles were heard over both lung fields. Heart rate was regular and no murmurs were heard. There was a moderately severe omphalitis with a purulent exudate. Fluoroscopic examination revealed both lung fields to be dark except at the base of the right lung. Further examination was omitted because of the critical condition of the patient.

Laboratory examination: Hemoglobin 20.2 Gm. or 139 per cent; red blood cells 4,200,000; white blood cells 25,000 with 7 per cent adult polymorphonuclears, 50 per cent immature polymorphonuclears, 17 per cent lymphocytes, 1 per cent monocytes, 25 per cent recorded as "myeloblasts". Platelets abundant on smear. Urine: clear, acid, 75–100 red blood cells and 10 white blood cells per low power field, no casts. Reports of cultures were as follows: stools, negative; throat swab, numerous alpha and beta streptococci. Nasopharyngeal swab, B. coli communior, negative for pneumocci. Cultures taken at postmortem: from umbilicus, B. coli communior; blood, alpha streptoccoccus fecalis and B. coli communior; spinal fluid, negative.

Course in hospital: Temperature was 35°C. on admission and fell to 34.4°C. terminally the same day. The patient was given oxygen continuously, sulfadiazine 1 Gm. stat and 0.25 Gm. every four hours, and supportive therapy. Breathing remained rapid and labored, and the pallor did not improve. At 6:30 p.m. the infant did not respond to stimuli; at 7:30 p.m. he died. Blood sulfadiazine level was 3.7 mgm. per cent.

It was thought that the child was suffering from pulmonary atelectasis with extensive pneumonia, an intracranial lesion, septicemia

from an umbilical infection, or pneumonia, singly or in some combination.

Family history: The pregnancy and labor of the mother had been uneventful. It has been impossible to obtain more information.

Autopsy: (No. 17631) The body is that of a moderately well nourished 10 day old infant weighing 3000 Gm. and measuring 51.5 cm. crown-heel length. There is inflammation of the umbilicus from

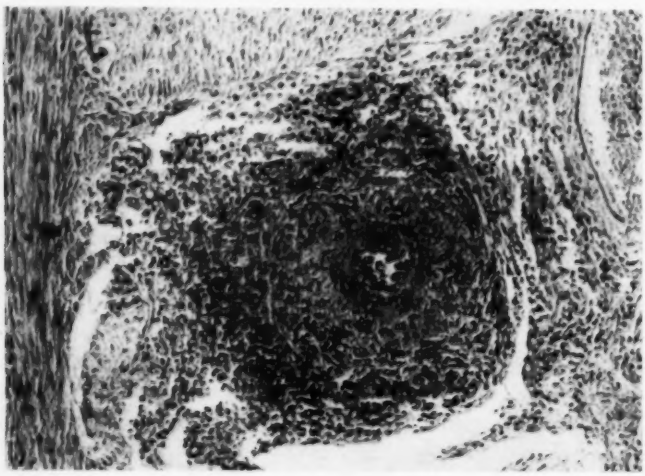


FIG. 3. PHOTOMICROGRAPH OF LESION OF PERIARTERITIS NODOSA FROM SMALL INTESTINE IN CASE II (AUTOPSY 17631)

The adventitial infiltration can be seen around the small artery with necrotic hyaline media.

which a purulent exudate is expressed. The heart weighs 28 Gm. and, except for a few small subepicardial petechiae, is normal. Both lungs are deep red color and somewhat collapsed. Hemorrhage is present; the left lung will not float in water. The liver, spleen, pancreas, adrenals, intestine, and mesentery are grossly normal. Each kidney weighs 20 Gm. and shows numerous hemorrhagic areas in the cortex and medulla, which resemble hemorrhagic infarcts grossly. The lines of ossification in the ribs are normal. Lymph nodes are not enlarged, and the brain is grossly normal. The spinal

fluid protein is 73 mgm. per cent. Crenated red cells are seen microscopically.

Microscopic examination: In the section of the umbilicus there is a superficial ulcer with underlying vascular granulation tissue, and polymorphonuclear leucocytes. The intima and media of the umbilical artery are completely necrotic with a few mononuclears and polymorphonuclear leucocytes surrounding the vessel. A nearby umbilical vein contains a thrombus.

In the small arteries about the adrenals, in the submucosa of the intestine and around the epididymis there are typical lesions of periarteritis nodosa characterized by edema of the media with spreading of the muscle fibers in the early stages, and, in some vessels, necrosis, fibrinoid alteration and hyalinization of the media, with infiltration of inflammatory cells in the adventia and media. Most of these cells are mononuclears, but some are polymorphonuclears neutrophilic and eosinophilic leucocytes. Proliferation of intimal endothelium is also seen.

In both kidneys there are large wedges with necrotic tubules which represent infarcts. A thrombus is seen in one of the interlobar renal arteries.

In the heart there are numerous small perivascular scars with many anitschkow cells. In the lungs there is extensive hemorrhage with fibrin and some mononuclear phagocytes in the alveoli. In one section aspirated stomach contents is seen in a large bronchus. In the liver there is a considerable amount of fat, distributed in fine droplets. No evidence of leucemia is found. The brain is normal.

DISCUSSION

Two cases of periarteritis nodosa reported here bring the total number of reported instances in the first year of life to four. In the case of periarteritis in a two and one-half month old infant reported by Kryzyszkowski (1) the differential diagnosis entertained by the clinicians was scarlet fever or syphilis. There was an indefinite skin rash, slight edema of the eyelids and extremities, and a fever of 40°C. The child died 11 days following the onset of symptoms and postmortem examination revealed small miliary aneurysms with thrombi in the coronary arteries. There was bronchopneumonia, nephritis,

chronic enteritis, "splenic tumor", and atelectasis. Microscopically the coronary lesions revealed the characteristic picture of periarteritis nodosa.

A case of periarteritis was found in a nine months old child by Thinnes (2). There were no symptoms until about 4 hours before death when sudden severe abdominal pains were manifest. Examination at that time was essentially negative. At necropsy multiple infarcts were found in the kidneys. The thymus weighed 34 Gm. and there were multiple areas of cardiac fibrosis in the left ventricle, which were considered the likely cause of death. Microscopic examination revealed extreme lesions of periarteritis nodosa in the kidney and heart.

Rothstein and Welt (7) reviewed the literature between 1866, when the disease was first described, and 1933, and found that out of a total of 195 cases of periarteritis nodosa reported, 23 occurred in children up to the age of 15 years. Keith and Baggenstoss (8) found that in the subsequent seven year period, up to 1941, 21 cases had been reported in childhood bringing the total to 44 cases. They found the most important clinical signs of this condition to be: fever, leucocytosis, abdominal pain, arthralgia, and evidence of renal disease. In some cases there were convulsions, generalized weakness, anemia, purpura, urticaria, hypertension, peripheral gangrene and tachycardia. Palpable nodules were found in only two children.

In the first case described in the present report the only pertinent clinical signs, in retrospect, were the purpura, the slight hematuria and the evidence of pains; in the second case even these slight clues were not present.

In the first case the precise nature of the inflammatory necrotic mass involving the right adrenal is difficult to decide, although numerous microscopic sections were prepared from various parts of it. While there are infarct-like shadows of adrenal tissue in places, the mass seems much too large to represent a simple hemorrhagic infarct. Moreover, it is not merely a mass of blood and necrotic adrenal tissue: there are abscess-like areas containing bacteria in it. It is difficult to escape the belief that there is some association between this inflammatory mass and the widespread periarteritis nodosa, but what that association may be is not clear.

In the second case there was an umbilical infection, and no other discovered adventitious circumstances. Since this infant was only 10 days old it is conceivable that the lesions may have developed *in utero*. It was not possible to trace the mother to determine her fate. It may be recalled that anaphylactic hypersensitivity is transferable from mother to foetus *in utero*. Ratner and his coworkers have demonstrated that the guinea pig foetus can be sensitized to foreign proteins either by injecting the antigen into the mother or by feeding the pregnant females protein foods foreign to their diet (11). The question of passage of foreign proteins through human breast milk remains controversial.

SUMMARY AND CONCLUSIONS

Two cases of periarteritis nodosa, one dying at ten days of life and the other at thirty-seven days are reported as the youngest cases in the literature. In one case there was an umbilical infection; in the other there was a large inflammatory-necrotic mass involving the right adrenal containing large numbers of unidentified cocci.

Symptoms of vomiting, abdominal pain, edema and purpura, together with fever and leucocytosis were manifest in the first case. Vomiting, dyspnea, pallor, and leucocytosis characterized the clinical picture of the second case. In both instances the disease ran a fulminating course, and the diagnosis was not suspected before autopsy.

Acknowledgement: I am indebted to Dr. Edwards A. Park for permission to use the clinical information in both cases. The photomicrographs were made by Miss Violet Crane.

BIBLIOGRAPHY

1. Krzyszkowski, J.: Periarteritis nodosa, Przeglad Lakarski, pp. 30, 45, 58, 1899.
2. Thinnes, P.: Periarteritis nodosa bei einem Saügling, Frankfurt. Ztschr. f. Path., **30:** 104, 1924.
3. Rich, A. R.: The rôle of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulphonamide therapy, Bull. Johns Hopkins Hosp., **71:** 123, 1942.
4. ———: Additional evidence of the rôle of hypersensitivity in the etiology of periarteritis nodosa; another case associated with a sulphonamide reaction, Bull. Johns Hopkins Hosp., **71:** 375, 1942.

5. Rich, A. R., and Gregory, J. E.: Experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp., **72:** 65, 1943.
6. ——— — ———: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity, **73:** 239, 1943.
7. Rothstein, J. L., and Welt, S.: Periarteritis nodosa in infancy and childhood; report of two cases with necrospy observations; abstracts of cases in the literature, Am. J. Dis. Child., **45:** 1277, 1933.
8. Keith, H. M., and Baggenstoss, A. H.: Primary arteritis (periarteritis nodosa) among children, J. Pediat. **18:** 494, 1941.
9. Rich, A. R., and Gregory, J. E.: On the anaphylactic nature of rheumatic pneumonitis, Bull. Johns Hopkins Hosp., **73:** 465, 1943.
10. Ratner, B., Jackson, H. C., and Gruehl, H. L.: Transmission of protein hypersensitiveness from mother to offspring, J. Immunol., **14:** 249, 1927, ibid., **14:** 267, 1927, ibid., **14:** 275, 1927, ibid., **14:** 291, 1927, ibid., **14:** 303, 1927.
11. Ratner, B.: Placental transmission of alimentary anaphylaxis, Proc. Soc. Exper. Biol., and Med., **30:** 88, 1932.